4/15/02

Michigan Department of Environmental Quality

Environmental Response Division

PART 201 CHEMICAL CRITERIA WORKSHEET

Developed under the authority of the

NATURAL RESOURCES AND ENVIRONMENTAL PROTECTION ACT, 1994 PA 451, AS AMENDED

All criteria are expressed in units of parts per billion (ug/L or ug/Kg).

Chemical:	2,3,7,8-Tetrachlorodibenzo-p-dioxin {O}	CAS #:	1746016
Synonyms:	TCDD; dioxin		
Sort name:	Tetrachlorodibenzo dioxin 2,3,7,8	Class:	Dioxin Class #: 10
IRIS File Date:		HEAST File Date:	

Chronic RfD mg/kg-d:	NA	RfD Date:		RfD Source:	MDEQ/ERD
SubChronic RfD mg/kg-d:		SubChronic RfD Date		SubChronic RfD Source:	

☐ Developmental Effector ☐ Reproductive Effector

RfD Details:

Oral SF (mg/kg-d)$^{-1}$	7.5E+4	Oral SF Date:	10/11/1999	Oral SF Souce:	MDEQ/TSG

EPA Classification:

IARC Classification: Group 1: Carcinogenic to humans

Other Classification: IIB - proposed upgrade to IIA (9th Report on Carcinogens)

Oral SF Details: Based on Pathology Working Group (PWG) reevaluation of Kociba liver and tumor data. Considering the insignificant difference between this and the old SF (1.56E+5) and EPA's current review of dioxin data, they have not adopted the new SF, but consider it scientifically valid. SWQD also considers it scientifically valid but are not adopting it for similar reasons. Since it is based on current pathology criteria it is being used here. It represents total significant tumor risk in female rats (Kociba et al., 1978). *All other dioxin isomers identified on site should be converted to TEF equivalents and compared to the criteria

Chronic RfC ug/m^3	NA	Chronic RfC Date:		Chronic RfC Source	
SubChronic RfC ug/m^3		SubChronic RfC Date		SubChronic RfC Sourc	

RfC Details:

IUR (ug/m^3)$^{-1}$	4.4E+1	IUR Date:	05/29/1992	IUR Source:	AQD/EPA

IUR Details: Potency based on EPA's CAG 1985 oral slope factor of 1.56 E5 (mg/kg)-1. Reviewed by DNR's TSG 7/12/90. 5/29/92 - awaiting EPA review to be completed before updating.

STEL ug/m^3	NA	STEL Date:		STEL Source:	

Sec 20101(1)(t) Hazardous Substance Determinaton: CERCLA Table 302.4

GENERIC CLEANUP CRITERIA FOR GROUNDWATER

Chemical: 2,3,7,8-Tetrachlorodibenzo-p-dioxin {O} CAS #: 1746016

Solubility ug/L 0.019 TDL in Water: 1.0E-5

DRINKING WATER CRITERIA

DW Date: 06/5/1995 Aesthetic DW: NA

MCL: 3E-5 RSC: 0.2

MCLG: State Drinking Water Standard: 3E-5

Res DWC: 3.0E-5 {A} Ind-Com DWC: 3.0E-5 {A}

Calc Res HBDW# Calc Ind-Com HBDW#

DW Notes:

GROUNDWATER SURFACE WATER INTERFACE CRITERIA

GSI Date: 04/22/1998 GSI: 1.0E-5 {M} GSI #: 1.0E-05

Rule 57 Drinking Water Value Rule 57 Drinking Water Value#:

FCV Formula: FCV Conversion Factor:

GSI Notes:

GROUNDWATER VOLATILIZATION TO INDOOR AIR INHALATION CRITERIA

GVIIC Date: 03/5/1998 Residential GVIIC: NLV Ind/Com GVIIC: NLV

Calc Residential GVIIC: 5.5E-01 Calc Ind/Com GVIIC: 3.0E+00

GROUNDWATER CONTACT CRITERION

GCC Date: 05/8/2001 GCC: 2.0E-5 {O,AA} GCC#: 0.00002

Calc GCC: 2.0E-05

GCC Notes: Filtered groundwater samples must be collected for appropriate comparison to the GCC.

FLAMMABILITY-EXPLOSIVITY AND ACUTE INHALATION SCREENING LEVELS

FESL/AISL Date: 01/1/1998 FESL: ID AISL: ID

FESL/AISL Notes: Calc FESL: Calc AISL:

GENERIC CLEANUP CRITERIA FOR SOIL

Chemical: 2,3,7,8-Tetrachlorodibenzo-p-dioxin {O}

CAS #: 1746016

Statewide Default Background: NA

TDL in Soil: 0.001

SOIL GROUNDWATER PROTECTION CRITERIA

GWPC Date: 05/3/2000

20 x Res DWC:	NLL	Res DWC SWPV:	NLL	Res DW PC:	NLL
Calc 20 x Res DWC:	6.0E-04	Calc Res DWC SWPV:	8.0E+00		
20x GSI Value:	NLL	GSI SWPV:	NLL	GSI PC:	NLL
Calc 20x GSI:	2.0E-04	Calc GSI SWPV:	2.7E+00		
20x GCC:	NLL	GCC SWPV:	NLL	GCC PC:	NLL
Calc 20x GCC:	2.0E-04	Calc GCC SWPV:	2.7E+00		
20x Ind-Com DWC:	NLL	Ind-Com DW SWPV:	NLL	Ind-Com DW PC:	NLL
Calc 20x Ind-Com DWC:	6.0E-04	Calc Ind-Com DW SWPV:	8.0E+00		
20x GSI DW:	NA	GSI DW SWPV:	NA	GSI DW PC:	NA
Calc 20x GSI DW:		Calc GSI DW SWPV:			

Leachability Determination: Chemical, due to its physiochemical properties, is not expected to leach through soils to groundwater under most conditions.

SOIL VOLATILIZATION TO INDOOR AIR INHALATION CRITERIA

SVIIC Date: 03/5/1998

Res SVIIC:	NLV	Ind/Com SVIIC:	NLV
Calc Res SVIIC:		CalcInd/Com SVIIC:	

SOIL INHALATION CRITERIA FOR AMBIENT AIR

SIC Date: 04/1/1998

Residential PSIC:	71 {O}	Ind/Com PSIC:	89 {O}		
Calc Residential PSIC:	7.1E+01	Calc Ind/Com PSIC:	8.9E+01		
Residential VSIC:	NLV	Ind/Com VSIC:	NLV		
Calc Residential VSIC:	2.6E+01	Calc Ind/Com VSIC:			
Res VSIC 5M:	NLV	Ind/Com VSIC 5M:	NLV	5 Meter Flux - 30 yr	1.23E-8
Calc Res VSIC 5M:	3.2E+01	Calc Ind/Com VISC 5M:	2.9E-02	5 Meter Flux - 21 yr	1.38E-8
Res VSIC 2M:	NLV	Ind/Com VSIC 2M:	NLV	2 Meter Flux - 30 yr	1.23E-8
Calc Res VSIC 2 M:	3.2E+01	Calc Ind/Com VISC 2M:	5.1E-02	2 Meter Flux - 21 yr	1.38E-8

SOIL SATURATION CONCENTRATION SCREENING LEVELS

Csat Date: 03/5/1998 Csat at 10 C: NA Calc Csat at 10 C:

SOIL DIRECT CONTACT CRITERIA

DCC Date: 11/27/2001 AEd: 0.03 AEi: 0.5 RSC for DCC: 1.0

Residential DCC:		Commercial III DCC:	0.92 {O}
Calc Res DCC:	1.5E-01	Calc Com III DCC:	9.2E-01
Industrial DCC:	0.74 {O}	Commercial IV DCC:	0.82 {O}
Calc Ind DCC:	7.4E-01	Calc Com IV DCC:	8.2E-01

CHEMICAL-SPECIFIC PROPERTIES

Chemical: 2,3,7,8-Tetrachlorodibenzo-p-dioxin {O}

CAS #: 1746016

Physical State at STP:	Solid	Water Solubility (ug/L):	0.019
Log Kow:	7.04	HLC (atm-m3/mol):	9.20E-6
Koc Equation Group:	1	Boiling Point (F):	
Calculated Koc (L/kg):	8.33E+6	Melting Point (C):	579
Kp:	Calculated	Vapor Pressure (mmHg):	0.0000000007372
Air diffusivity (cm2/s):	0.047	Molecular Weight (g/mol):	322
Water diffusivity (cm2/s):	8.0E-6	Flash Point (F):	NA
References:	HWIR	LEL (ug/m3) :	NA
		LEL Source:	

Koc's

Ionizing Organic: ☐

Koc (L/kg) for Ionizing Organics

pH 4.9:	NR
pH 6.8:	NR
pH 8.0:	NR

Kd (L/kg) for Inorganics

pH 4.9:	NR
pH 6.8:	NR
pH 8.0:	NR

Physical hazards:

Notes:
Rule 57# partial BPJ/CRV. Final MCL = 5E-5 ppb. 3% dermal absorption efficiency used as recommemded in EPA Dermal Exposure Assessment: Principles and Applications. No IRIS file, checked 11/29/94.

Criteria Update:	04/22/1998
File Update:	10/11/1999
Most Recent Tox Review:	06/20/1996
AQD CAS Date:	
ERD CAS Date:	
Initialized By:	RI

TSG Review Date:

PART 201 GENERIC SOIL DIRECT CONTACT CRITERIA TECHNICAL SUPPORT DOCUMENT

Michigan Department of Environmental Quality
Environmental Response Division

January 5, 2001

This technical support document (TSD) presents the methodology for development of the Part 201 generic soil direct contact criteria (DCC) pursuant to Sections 20120a(1)(a),(b), and (d) and 20120(a)(3) of Part 201, Environmental Remediation, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended. It also provides information about the implementation of the soil DCC. This document replaces the soil DCC TSD dated August 31, 1998.

The soil DCC as represented in this TSD are presented in the Environmental Response Division Operational Memorandum #18: Part 201 Generic Cleanup Criteria Tables, Revision 1 dated June 7, 2000. The Residential and Commercial I DCC are presented in column #19 of the Soil: Residential and Commercial I Table. The Industrial and Commercial II, Commercial III, and Commercial IV DCC are presented in columns #27, #28, and #29, respectively, of the Soil: Industrial and Commercial II, III, and IV Table.

IMPLEMENTATION OF THE DIRECT CONTACT CRITERIA

The soil DCC represent a soil concentration that is protective against adverse health effects due to long-term ingestion of and dermal contact with contaminated soil. DCC which are lower than the target detection limit (TDL) or background, default to the TDL or background. For hazardous substances with criteria greater than their respective soil saturation concentrations (Csat), the criterion defaults to Csat unless a facility-specific demonstration has been made that soils with concentrations greater than Csat do not contain free-phase contaminant. Refer to the Csat TSD (MDEQ, 1998) for details on how this demonstration may be made.

Remedial Action Plans (RAPs) based on soil DCC cannot be approved without a demonstration that all other relevant pathways have been addressed. Since the soil DCC only address long-term ingestion of and dermal contact with contaminated soil, and criteria are not available which address all potential public health or environmental hazards, other concerns may need to be addressed. These types of concerns are noted and discussed in Operational Memorandum #18 (MDEQ, 2000).

Compliance with soil DCC is required throughout the affected medium for generic land use categories, but exposure controls and land use restrictions may be employed to prevent exposures to more highly contaminated soils under the limited land use categories. Facility-specific generic or site-specific DCC may also be developed.

Average on-site soil concentrations, represented as a 95 percent upper confidence level (UCL) on the arithmetic mean, may be used to determine compliance with the soil DCC. On-site 95 percent UCLs should, however, reasonably represent the areas over which exposures are expected to occur. Typically, the exposure area for a residential property is approximately one-quarter acre in size. The distribution of the data (i.e., normal, lognormal or other) must be identified before the 95 percent UCL can be properly calculated. Refer to United States

Environmental Protection Agency (EPA) guidance on how to appropriately calculate the 95 percent UCL (EPA, 1992a). Sample results from hot spots or significantly elevated areas should be addressed separately and not included in the calculation of the 95 percent UCL.

GENERAL INFORMATION ABOUT THE DIRECT CONTACT ALGORITHMS

The equations yield values that represent concentrations of contaminants in soil in units of micrograms per kilogram (ug/kg) or parts per billion (ppb). To convert to units of parts per million or milligrams per kilogram (mg/kg) in soil, divide by 1,000.

The acceptable level of risk for carcinogens is one in one hundred thousand (10^{-5}). Exposure to noncarcinogens is evaluated through the use of a target hazard quotient (THQ). The THQ is the ratio of a single substance's exposure level over a specified time period to a reference dose for that substance derived from a similar exposure period. An acceptable THQ is equal to or less than one. A THQ > 1 indicates an unacceptable exposure (i.e., the exposure level is greater than the reference dose).

Reasonable Maximum Exposure

The EPA provides general guidance on how to characterize exposures and risks when conducting risk assessments. For exposure assessments, intake and exposure values should be selected so that the combination of all variables results in an estimate of the reasonable maximum exposure (RME) for that pathway. The RME is the maximum exposure that is reasonably expected to occur at a site. Under this approach, some intake variables may not be at their individual maximum values, but when in combination with other variables, will result in estimates of the RME (EPA, 1989). EPA guidance (EPA, 1992b), recommends estimating the high-end exposure by "...identifying the most sensitive parameters and using maximum or near-maximum values for one or a few of these variables, leaving others at their mean values." This guidance applies when only limited information on the distribution of the exposure or dose factors is available. This recommendation is based on the fact that maximizing all variables will result in an estimate that is above the range of actual values seen in the population. The algorithms presented in this document follow EPA guidance by combining exposure assumptions which represent a mix of high-end and mid-range values. More specifically, a 70 year life span, body weight and surface area all represent a 50th percentile, while the exposure duration of 21 years and the soil ingestion rate represent 90th percentile values.

Averaging Time

The selection of an appropriate averaging time (AT) is dependent upon the type of toxic effect being evaluated. AT represents the number of days over which the exposure is averaged. When evaluating long-term exposure to noncarcinogenic compounds, exposures are calculated by averaging over the period of exposure (i.e., subchronic or chronic exposures). The approach for developmental toxicants is different. Since one dose of a developmental toxicant can cause adverse effects (particularly during organogenesis), the acceptable daily dose should not be averaged. That is, AT and the exposure parameters [exposure frequency (EF) and exposure duration (ED)] for developmental toxicants should equal 1. For carcinogenic compounds, exposures are calculated by prorating the total cumulative dose over a lifetime (also called lifetime average daily dose). The approach for carcinogens is based on the assumption that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over a lifetime.

(4) If a revised land use-based remedial action includes characteristics that are required by R 299.5532 to be approved by the department, then the person implementing the change shall seek department approval as required by part 201 of the act and these rules.

(5) The horizontal and vertical extent of hazardous substance concentrations in an aquifer above the higher of either the concentration allowed by Section 20120a(1)(a) or (11) of the act, as applicable, shall not increase after the initiation of remedial actions to address an aquifer, except as approved by the director as provided in section 20118(5) and (6) of the act.

(6) All remedial actions that address the remediation of an aquifer shall provide for removal of the hazardous substance or substances from the aquifer, either through active remediation or as a result of naturally occurring biological or chemical processes which can be documented to occur at the facility, except as provided in section 20118(5) and (6) of the act.

R 299.5706 General requirements for application of cleanup criteria.

Rule 706. (1) All cleanup criteria used in remedial actions undertaken under part 201 of the act and these rules shall be based on best available information.

(2) The generic cleanup criteria developed by the department using the algorithms presented in part 7 of these rules are derived primarily from data that reflect chronic toxicity endpoints. If a hazardous substance has a more sensitive toxic effect than those associated with the chronic toxicity data used to calculate a generic criterion, then a criterion shall be developed to address the most sensitive effect. Except as provided in R 299.5532(9), generic cleanup criteria established by the department shall be accepted as protective of the most sensitive toxic effect in a given exposure pathway for the hazardous substance in question.

(3) If the department has not calculated a criterion for a hazardous substance for a given exposure pathway, then the person proposing or implementing the remedial action shall supply the necessary data for the department to calculate a criterion or establish a criterion under subrule (4) of this rule, unless the department determines that a numerical criterion is not required to assure that a given remedial action will be protective.

(4) A generic or site-specific cleanup criterion may be established by the department based on best professional judgment instead of a calculation based on minimum toxicity data for a specific hazardous substance when the minimum toxicity data are not available for that hazardous substance, but data of sufficient quality are available to show that the hazardous substance in question can be adequately assessed by comparison to the toxicity of another hazardous substance for which sufficient data are available. A criterion may be established by the department in this manner when the hazardous substances are expected by the department to have similar fate and toxicity.

R 299.5706a Generic cleanup criteria; toxicological and chemical-physical properties; use of generic cleanup criteria as risk based screening levels; procedure for developing additional generic criteria.

Rule 706a. (1) Except as provided in R 299.5532(9) and subrules (10), (11) and (12) of this rule, generic groundwater cleanup criteria for the residential, commercial and industrial categories shall be the values shown in table 1 of R 299.5744. If a generic groundwater cleanup criterion is higher than the flammability and explosivity screening level or the acute inhalation screening level shown in table 1 of R 299.5744, then the person proposing or implementing response activity shall document whether additional response activity is required to protect against those acute hazards.

(2) Except as provided in R 299.5532(9) and subrules (10), (11), and (12) of this rule, generic soil cleanup criteria for the residential and commercial i categories shall be the values shown in table 2 of R 299.5746.

(a) If a generic soil cleanup criterion is greater than C_{sat}, then the person proposing or implementing response activity shall document whether additional response activity is required to control free-phase liquids or to protect against hazards associated with free-phase liquids that are not accounted for in development of the generic criteria.

(3) Except as provided in R 299.5532(9) and subrules (10), (11), and (12) of this rule, generic soil cleanup criteria for the commercial II, III, IV, and industrial categories shall be the values shown in table 3 of R 299.5748.

(4) The generic cleanup criteria shown in R 299.5744, R 299.5746, and R 299.5748 and identified under subrule (14) of this rule may be used and known as risk-based screening levels for corrective actions required under the part 213 of the act.

(5) Generic cleanup criteria under R 299.5744, R 299.5746, and R 299.5748 are based on R 299.5707 in the following cases:

(a) If a calculated cleanup criterion is less than the target detection limit for that hazardous substance in a given medium, then the target detection limit is the cleanup criterion. Criteria to which this subdivision applies are designated with a footnote in the criteria tables.

(b) A background concentration may be substituted for a generic cleanup criterion when the background concentration is higher than a criterion shown in R 299.5744, R 299.5746, or R 299.5748.

(6) If a hazardous substance imparts adverse aesthetic characteristics to groundwater at a concentration less than the health-based criterion for that hazardous substance, the aesthetic-based criterion derived under R 299.5709 is shown as the drinking water criterion in the table of generic cleanup criteria in R 299.5744 and designated with a footnote.

(7) Except as provided in section 20120a(10) of the act and R 299.5750(1)(o), the toxicological and physical-chemical input values used by the department to derive generic cleanup criteria with the equations and default assumptions provided in R 299.5710, R 299.5712, R 299.5714, R 299.5720, R 299.5722, R 299.5724, and R 299.5726 are shown in table 4 of R 299.5752.

(8) Toxicological and chemical-physical data in table 4 of R 299.5752, if available, shall be used in conjunction with the equations and default assumptions that appear in these rules for the development of generic cleanup criteria under

subrule (10) or (11) of this rule, except as provided in section 20120a(10) of the act and R 299.5750(1)(o).

(9) Except as provided in subdivision (a) of this subrule, site-specific cleanup criteria developed under section 20120a(2) of the act shall use the toxicological and chemical-physical data in table 4 of R 299.5752, or shall be based on the procedures allowed for under subrules (10) and (11) of this rule. Site-specific assumptions may be substituted for the default assumptions specified in R 299.5710, R 299.5712, R 299.5714, R 299.5720, R 299.5722, R 299.5724, and R 299.5726, if appropriate; however, the equations presented in the pertinent rule shall be used to calculate site-specific criteria. Non-human health based toxicological values may be modified through the development of site-specific cleanup criteria under section 20120a(2) of the act and R 299.5716(11).

(a) The following chemical-physical properties may be modified as part of a site-specific cleanup criterion developed under section 20120a(2) of the act, if documented by the person proposing the site-specific criterion to be more appropriate for a specific facility than the generic parameter listed in table 4 of R 299.5752:

(i) Relative source contribution factor for drinking water.

(ii) Ingestion absorption efficiency.

(iii) Dermal absorption efficiency.

(iv) Relative source contribution factor for soil.

(v) Soil k_{oc} for ionizing organic compounds.

(vi) Soil-water distribution coefficients for inorganic compounds.

(10) For a substance that is not listed in the cleanup criteria tables in R 299.5744, R 299.5746, or R 299.5748, the department may determine if the substance is a hazardous substance using best available information about the toxicological and physical-chemical properties of that substance and use that information to develop a generic or site-specific cleanup criterion.

(11) For a substance that is listed in the cleanup criteria tables in R 299.5744, R 299.5746, or R 299.5748, if the department obtains sufficient information to support calculation of a cleanup criterion which is designated in the cleanup criteria tables or table 4 of R 299.5752 with a footnote "ID" or "NA," the department shall use best available information to calculate a cleanup criterion for the hazardous substance.

(12) If a new state drinking water standard is established or a state drinking water standard is changed after the effective date of this rule, the drinking water standard in effect under section 5 of 1976 pa 399, MCL 325.1005 et seq. shall become the generic residential cleanup criterion under R 299.5744, as provided in section 20120a(5) of the act.

(13) If a generic cleanup criterion is developed under subrule (10) or (11) of this rule, or modified under subrule (12) of this rule, the department shall make the new toxicological and physical-chemical data and criterion available by announcing it on the department's internet web site, and by publishing notice of the change in the department calendar, or by such other means that effectively notifies interested persons. The new criterion shall take effect when published and announced by the department as called for in this rule. The new data and resulting cleanup criterion

TABLE 4. TOXICOLOGICAL AND CHEMICAL-PHYSICAL DATA FOR PART 201 GENERIC CLEANUP CRITERIA AND SCREENING LEVELS

Scientific notation is represented by E+ or E- a value, for example 2 x 10^6 is reported as 2.0E+6.
Units are as indicated in each column heading. The dataset for each hazardous substance requires 22 columns.
Review all 22 columns, on 2 pages, when evaluating data for a specific hazardous substance.

Hazardous Substance	Chemical Abstract Service Number (CAS#)	Oral Reference Dose (RfD)	Oral Slope Factor (SF)	Initial Threshold Screening Level (ITSL)	Inhalation Unit Risk Factor (IURF)	Occupational Short Term Exposure Level (STEL)	Relative Source Contribution for Drinking Water (RSC)	Ingestion Absorption Efficiency (AEi)	Dermal Absorption Efficiency (AEd)	Relative Source Contribution for Soil (RSC)	Log Octanol-Water Partition Coefficient (Log Kow)
		mg/kg-day	$(mg/kg\text{-}day)^{-1}$	ug/m^3	$(ug/m^3)^{-1}$	ug/m^3	unitless	unitless	unitless	unitless	unitless
Acenaphthene	83329	1.8E-1	NA	2.1E+2	NA	NA	0.2	1.0	0.1	1.0	3.92
Acenaphthylene	208968	7.1E-3	NA	3.5E+1	NA	NA	0.2	1.0	0.1	1.0	3.6
Acetaldehyde	75070	1.3E-1	NA	9.0E+0	2.2E-6	4.5E+4	0.2	1.0	0.1	1.0	-0.367
Acetic acid	64197	5.7E-1	NA	2.5E+2	NA	3.7E+4	0.2	1.0	0.1	1.0	-0.23
Acetone	67641	1.0E-1	NA	5.9E+3	NA	1.782E+6	0.2	1.0	0.1	1.0	-0.240
Acetonitrile	75058	1.9E-2	NA	6.0E+1	NA	1.01E+5	0.2	1.0	0.1	1.0	-0.337
Acetophenone	98862	2.1E-1	NA	4.9E+2	NA	NA	0.2	1.0	0.1	1.0	1.6
Acrolein	107028	1.6E-2	NA	2.0E-2	NA	6.9E+2	0.2	1.0	0.1	1.0	-0.01
Acrylamide	79061	2.0E-4	2.8E+0	NA	1.3E-3	NA	0.2	1.0	0.1	1.0	-0.96
Acrylic acid	79107	5.3E-1	NA	1.0E+0	NA	NA	0.2	1.0	0.1	1.0	0.35
Acrylonitrile	107131	NA	3.3E-1	2.0E+0	6.8E-5	NA	0.2	1.0	0.1	1.0	0.255
Alachlor	15972608	1.0E-2	9.6E-2	NA	NA	NA	0.2	0.5	0.1	1.0	3.52
Aldicarb	116063	1.0E-3	NA	NA	NA	NA	0.2	1.0	0.1	1.0	1.1
Aldicarb sulfoxide	1646873	1.3E-3	NA	NA	NA	NA	0.2	1.0	0.1	1.0	-0.67
Aldicarb sulfone	1646884	1.1E-3	NA	NA	NA	NA	0.2	1.0	0.1	1.0	-0.57
Aldrin	309002	2.5E-5	8.7E+0	NA	4.9E-3	NA	0.2	0.5	0.1	1.0	6.5
Aluminum	7429905	3.3E-1	NA	NA	NA	NA	0.2	0.5	0.01	1.0	NR
Ammonia	7664417	NA	NA	1.0E+2	NA	2.4E+4	0.2	1.0	0.1	1.0	NA
t-Amyl methyl ether (TAME)	994058	1.3E-1	NA	6.2E+1	NA	NA	0.2	1.0	0.1	1.0	1.73
Aniline	62533	NA	1.6E-2	1.0E+0	NA	NA	0.2	1.0	0.1	1.0	0.978

TABLE 4. TOXICOLOGICAL AND CHEMICAL-PHYSICAL DATA FOR PART 201 GENERIC CLEANUP CRITERIA AND SCREENING LEVELS

Hazardous Substance	Chemical Abstract Service Number (CAS#)	Oral Reference Dose (RfD)	Oral Slope Factor (SF)	Initial Threshold Screening Level (ITSL)	Inhalation Unit Risk Factor (IURF)	Occupational Short Term Exposure Level (STEL)	Relative Source Contribution for Drinking Water (RSC)	Ingestion Absorption Efficiency (AEi)	Dermal Absorption Efficiency (AEd)	Relative Source Contribution for Soil (RSC)	Log Octanol-Water Partition Coefficient (Log Kow)
		mg/kg-day	$(mg/kg\text{-}day)^{-1}$	ug/m^3	$(ug/m^3)^{-1}$	ug/m^3	unitless	unitless	unitless	unitless	unitless
Sodium	17341252	3.4E+1	NA	NA	NA	NA	0.1	0.5	0.01	1.0	NR
Strontium	7440246	6.3E-1	NA	NA	NA	NA	0.2	0.5	0.01	1.0	NR
Styrene	100425	2.0E-1	1.3E-2	1.0E+3	5.7E-7	1.7E+5	0.2	1.0	0.1	1.0	2.94
Sulfate	14808798	NA	NA	NA	NA	NA	NA	0.5	0.1	1.0	NR
Tebuthiuron	34014181	7.0E-2	NA	NA	NA	NA	0.2	1.0	0.1	1.0	1.78
2,3,7,8-Tetrabromodibenzo-p-dioxin	50585416	NA	NA	NA	NA	NA	0.2	0.5	0.03	1.0	7.24
1,2,4,5-Tetrachlorobenzene	95943	3.4E-1	NA	NA	NA	NA	0.2	1.0	0.1	1.0	4.64
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746016	NA	NA	NA	NA	NA	0.2	0.5	0.03	0.2	7.04
1,1,1,2-Tetrachloroethane	630206	8.9E-2	1.1E-2	NA	7.4E-6	NA	0.2	1.0	0.1	1.0	2.63
1,1,2,2-Tetrachloroethane	79345	NA	1.0E-1	NA	5.8E-5	NA	0.2	1.0	0.1	1.0	2.39
Tetrachloroethylene	127184	1.0E-2	2.6E-2	NA	5.8E-7	6.85E+5	0.2	1.0	0.1	1.0	2.67
Tetrahydrofuran	109999	1.3E-2	NA	5.9E+3	NA	7.37E+5	0.2	1.0	0.1	1.0	0.46
Tetranitromethane	509148	NA	NA	NA	1.5E-2	NA	0.2	1.0	0.1	1.0	-2.05
Thallium	7440280	6.7E-5	NA	NA	NA	NA	0.2	0.5	0.01	1.0	NR
Toluene	108883	2.2E-1	NA	4.0E+2	NA	NA	0.2	1.0	0.1	1.0	2.75
p-Toluidine	106490	NA	5.6E-2	NA	3.1E-5	NA	0.2	1.0	0.1	1.0	1.39
Toxaphene	8001352	NA	4.4E-1	NA	3.2E-4	1.0E+3	0.2	0.5	0.1	1.0	5.5
Triallate	2303175	1.3E-2	NA	NA	NA	NA	0.2	1.0	0.1	1.0	4.57
Tributylamine	102829	3.5E-3	NA	7.0E+0	NA	NA	0.2	1.0	0.1	1.0	4.46
1,2,4-Trichlorobenzene	120821	1.5E-2	NA	3.7E+2	NA	3.7E+4	0.2	1.0	0.1	1.0	4.01
1,1,1-Trichloroethane	71556	2.2E+0	NA	1.0E+3	NA	2.46E+6	0.2	1.0	0.1	1.0	2.48
1,1,2-Trichloroethane	79005	3.9E-3	2.9E-2	NA	1.6E-5	NA	0.2	1.0	0.1	1.0	2.05

TABLE 4. TOXICOLOGICAL AND CHEMICAL-PHYSICAL DATA FOR PART 201 GENERIC CLEANUP CRITERIA AND SCREENING LEVELS

Hazardous Substance	Chemical Abstract Service Number (CAS#)	Soil Organic Carbon-Water Partition Coefficients for Organic Compounds (Koc)	Soil K_{oc} for Ionizing Organic Compounds at pH=6.8	Soil-Water Distribution Coefficients for Inorganic Compounds at pH=6.8 (Kd)	Henry's Law Constant at 25°C (HLC)	Air Diffusivity (D_i or D_a or D^{air})	Water Diffusivity (D_w)	Lower Explosive Limit in Air (LEL)	Flash Point (FP)	Water Solubility (S)	Physical State Identifier	Molecular Weight (MW)
		L/kg	L/kg	L/kg	atm-m^3/mol	cm^2/s	cm^2/s	unitless	°F	ug/L		g/mol
Sodium	17341252	NR	NR	NA	NR	NR	NR	NA	NA	NA	Inorganic	23
Strontium	7440246	NR	NR	NA	NR	NA	NA	NA	NA	NA	Inorganic	87.62
Styrene	100425	777	NR	NR	2.75E-3	0.071	8.0E-6	0.009	88	3.10E+5	Liquid	104.15
Sulfate	14808798	NR	NR	NA	NR	0.08	8.0E-6	NA	NA	NA	Inorganic	96.066
Tebuthiuron	34014181	56.2	NR	NR	2.40E-10	0.08	8.0E-6	NA	NA	2.50E+6	Solid	228.31
2,3,7,8-Tetrabromodibenzo-p-dioxin	50585416	1.31E+7	NR	NR	2.95E-7	0.08	8.0E-6	NA	NA	0.00996	Solid	499.6
1,2,4,5-Tetrachlorobenzene	95943	36,400	NR	NR	1.20E-3	0.08	8.0E-6	NA	NA	1,300	Solid	215.28
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746016	8.33E+6	NR	NR	9.20E-6	0.047	8.0E-6	NA	NA	0.019	Solid	322
1,1,1,2-Tetrachloroethane	630206	145	NR	NR	2.40E-3	0.071	7.9E-6	NA	NA	1.10E+6	Liquid	167.85
1,1,2,2-Tetrachloroethane	79345	93.5	NR	NR	3.45E-4	0.071	7.9E-6	NA	NA	2.97E+6	Liquid	167.85
Tetrachloroethylene	127184	156	NR	NR	1.84E-2	0.072	8.2E-6	NA	NA	2.0E+5	Liquid	165.83
Tetrahydrofuran	109999	2.83	NR	NR	9.63E-3	0.08	8.0E-6	0.02	6.0	1.0E+9	Liquid	72.12
Tetranitromethane	509148	9.66E-3	NR	NR	2.6E-05	0.08	8.0E-6	NA	NA	85,000	Liquid	196.03
Thallium	7440280	NR	NR	71	NR	NR	NR	NA	NA	NA	Inorganic	204.383
Toluene	108883	180	NR	NR	6.64E-3	0.087	8.6E-6	0.011	40	5.26E+5	Liquid	92.14
p-Toluidine	106490	23.3	NR	NR	6.10E-6	0.08	8.0E-6	NA	188	7.60E+6	Liquid	107.17
Toxaphene	8001352	2.55E+5	NR	NR	6.00E-6	0.0116	4.34E-6	NA	NA	740	Solid	414
Triallate	2303175	31,100	NR	NR	1.93E-5	0.08	8.0E-6	NA	NA	4,000	Liquid	304.66
Tributylamine	102829	24,200	NR	NR	5.60E-3	0.08	8.0E-6	NA	NA	75,400	Liquid	185.4
1,2,4-Trichlorobenzene	120821	1,790	NR	NR	1.42E-3	0.03	8.23E-6	NA	222	3.00E+5	Liquid	181.45
1,1,1-Trichloroethane	71556	110	NR	NR	1.72E-2	0.078	8.8E-6	0.075	NA	1.33E+6	Liquid	133.4
1,1,2-Trichloroethane	79005	50.3	NR	NR	9.13E-4	0.078	8.8E-6	0.06	NA	4.42E+6	Liquid	133.4

establishing levels that are protective of the public health, safety, and welfare and the environment.

(3) The department may calculate generic cleanup criteria for certain hazardous substances using exposure assumptions other than those shown in the algorithms in part 7 of these rules if either of the following conditions is satisfied:

(a) A hazardous substance causes an adverse effect in a sensitive subpopulation that is not adequately protected or represented by the generic exposure assumptions.

(b) The toxicokinetics of a hazardous substance are not best represented by the average daily dose, when accounting for the most sensitive effect.

R 299.5736 Minimum toxicity data for calculation of criteria based on noncarcinogenic endpoints.

Rule 736. (1) The minimum data required to calculate a cleanup criterion for a noncarcinogen when the route of exposure is ingestion or dermal absorption shall be the reference dose that is determined on the basis of the best available information and considering the weight of evidence.

(2) The minimum data required to calculate a cleanup criterion for a noncarcinogen when the route of exposure is inhalation shall be the minimum data required for calculation of an initial threshold screening level developed under part 55 of the act, and rules promulgated under part 55.

R 299.5738 Determination of cancer slope factors for use in calculation of criteria based on carcinogenic endpoints.

Rule 738. (1) A non-threshold mechanism of carcinogenesis shall be assumed unless biological data adequately demonstrate the existence of a threshold on a hazardous substance-specific basis.

(2) All appropriate human epidemiologic data, animal cancer bioassay data, and all other pertinent data shall be considered and a cancer slope factor developed if the weight of evidence for carcinogenicity is sufficient. Preferred data are those from studies which use the same route of exposure addressed by the criteria. However, in the absence of such data, route-to-route extrapolations may be conducted where appropriate, considering whether the critical effect is systemic and thus possible for each different route of exposure. The risk-associated dose shall be set at a level corresponding to an increased cancer risk of 1 in 100,000. If acceptable human epidemiologic data are available for a hazardous substance, then those data shall be used to derive the risk-associated dose. If acceptable human epidemiologic data are not available, then the risk-associated dose shall be derived from available animal bioassay data. Data from a species that is considered most biologically relevant to humans, that is, responds most like humans, is preferred where all other considerations regarding quality of data are equal. In the absence of data to distinguish the most relevant species, data from the most sensitive species tested,

that is the species showing a carcinogenic effect at the lowest administered dose, shall generally be used.

(3) If animal bioassay data are used and a non-threshold mechanism of carcinogenicity is assumed, then the data shall be fitted to a linearized multistage model, for example, a Global '86 or equivalent computer model. Global '86 is the linearized multistage model that was derived by Howe, Crump, and Van Landingham (1986), which was prepared for the United States environmental protection agency under subcontract 2-251u-2745 to Research Triangle Institute, contract 68-01-6826, and which the United States environmental protection agency uses to determine cancer potencies. The upper-bound 95% confidence limit on risk, or the lower 95% confidence limit on dose, at the 1 in 100,000 risk level shall be used to calculate a risk-associated dose for individual hazardous substances. Other models, including modifications or variations of the linearized multistage model that are more appropriate to the available data may be used where scientifically justified.

(4) If the duration of the study is significantly less than the natural lifespan of the test animal, then the slope factor may be adjusted on a case-by-case basis to compensate for latent tumors that were not expressed. The lifespan of a rat is assumed to be 104 weeks and the lifespan of a mouse is assumed to be 90 weeks. If the test animal is a rat and the study duration is less than 90 weeks, or if the test animal is a mouse and the study duration is less than 78 weeks, then the slope factor shall be multiplied by the following factor: the expected lifespan (L) divided by the study duration (L_e) raised to the third power, $[(L/L_e)^3]$.

(5) A species scaling factor shall be used to account for differences between test species and humans. It shall be assumed that scaling daily administered doses by body mass raised to the 3/4 power achieves equivalence in lifetime carcinogenic risk in different mammalian species. To derive a human slope factor from animal data, the default procedure shall be to multiply the animal slope factor by the ratio of human to animal body weights raised to the 1/4 power. However, if adequate pharmacokinetic and metabolism studies are available, then these data may be factored into the adjustment for species differences on a case-by-case basis.

(6) Additional adjustments shall be made to the data as appropriate. For some cancer data sets, it may be appropriate to combine incidences of multiple tumor types or combine benign and malignant tumors of the same histogenic origin. All doses shall be adjusted to give an average daily dose over the study duration. Adjustments shall be made to the tumor incidence for early mortality. Animals dying before the appearance of the first tumor within their dose group shall be removed from the data set. Before quantification of the dose response, a goodness-of-fit evaluation of the data shall be conducted.

(7) If human epidemiologic data, animal bioassay data, or other biological data indicate that a chemical causes cancer via a threshold mechanism, then the risk-associated dose may, on a case-by-case basis, be calculated using a method that assumes a threshold mechanism is operative.

(8) Inhalation unit risk factors shall be calculated in the same manner as cancer risk screening levels for inhalation risk under part 55 of the act.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 13 1998

OFFICE OF
SOLID WASTE AND EMERGENCY RESPONSE

OSWER Directive 9200.4-26

MEMORANDUM

SUBJECT: Approach for Addressing Dioxin in Soil at CERCLA and RCRA Sites

FROM: Timothy Fields, Jr. Acting Administrator /s/
Office of Solid Waste and Emergency Response

TO: Director, Office of Site Remediation and Restoration
Region I
Director, Emergency and Remedial Response Division
Region II
Director, Division of Environmental Planning and Protection
Region II
Director, Hazardous Waste Management Division
Regions IX
Director, Waste Management Division
Region IV
Director, Waste, Pesticides, & Toxics Division
Region V
Director, RCRA Multimedia Planning & Permitting Division
Region V
Director, Superfund Division
Regions III, V, VI, VII
Assistant Regional Administrator, office of Ecosystems Protection and Remediation
Region VIII
Director, Hazardous Waste Program
Region VIII
Director, Office of Environmental Cleanup
Region X
Director, Office of Waste and Chemical Management
Region X

PURPOSE

The purpose of this Directive is to recommend preliminary remediation goals (PRGs) or starting points for setting cleanup levels for dioxin in soil at Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) and Resource Conservation and Recovery Act (RCRA) corrective action sites. These recommended levels are to be used pending the release of the U.S. Environmental Protection Agency (EPA) comprehensive dioxin reassessment report and cross-program assessment of the impacts of the report. One ppb (TEQs, or toxicity equivalents) is to be generally used as a starting point for setting cleanup levels for CERCLA removal sites and as a PRG for remedial sites for dioxin in surface soil involving a residential exposure scenario. For commercial/industrial exposure scenarios, a soil level within the range of 5 ppb to 20 ppb (TEQs) should generally be used as a starting point for setting cleanup levels at CERCLA removal sites and as a PRG for remedial sites for dioxin in surface soil. These levels are recommended unless extenuating site-specific circumstances warrant a different level.

The dioxin levels discussed in this Directive are also generally recommended for actions taken under RCRA at corrective action sites. The recommended levels of 1 ppb (TEQs) for residential soils and within the range of 5 ppb to 20 ppb (TEQs) for commercial/industrial soils should generally be used as starting points in setting soil cleanup levels at RCRA corrective action sites. These levels are generally consistent with soil cleanup levels set at RCRA facilities throughout the country where dioxin is a principal contaminant of concern at the facility. However, because states are the primary implementors of the RCRA Corrective Action program, this Directive does not prescribe specific procedures for implementation under RCRA.

This Directive sets forth the policy basis for these recommended levels and prescribes procedures for implementing these recommendations.

BACKGROUND

To date, EPA has generally selected 1 ppb as a cleanup level for dioxin in residential soils at Superfund and RCRA cleanup sites where dioxin is a principal contaminant of concern at the facility. EPA has also, to date, generally selected a cleanup level for dioxin within the range of 5 ppb to 20 ppb for commercial/industrial soils at Superfund and RCRA cleanup sites where dioxin is a principal contaminant of concern at the facility. The levels that EPA has selected at these sites are protective of human health and the environment. Based on presently available information, and using standard default assumptions for reasonable maximum exposure scenarios, the upper-

bound lifetime excess cancer risk from residential exposure to a concentration of 1 ppb dioxin is approximately 2.5×10^{-4}, which is at the higher end of the range of excess cancer risks that are generally acceptable at Superfund sites. The calculated upper-bound excess cancer risk associated with a lifetime commercial/industrial exposure to 5 ppb, or the lower end of the range recommended for commercial/industrial soils, is approximately 1.3×10^{-4}, which is also within the CERCLA risk range. It should be noted that there is more difficulty in generalizing about the cancer risk associated with commercial/industrial cleanup levels than there is with residential cleanup levels due to the greater variability in exposures associated with commercial/industrial scenarios. Accordingly, the consultation process for Superfund sites referenced in the implementation section of this Directive should be used to ensure the selection of appropriate, protective dioxin levels at CERCLA commercial/industrial sites. Similarly, for RCRA corrective action sites, please refer to the implementation section of this Directive.

EPA is presently completing work on a comprehensive reassessment of the toxicity of dioxin, to be embodied in the documents entitled "Health Assessment Document for 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds" and "Estimating Exposure to Dioxin-like Compounds." The reassessment report, which is scheduled to be issued in 1998, will represent the culmination of an Agency-wide effort to collect, analyze and synthesize all of the available information about dioxin. It has undergone significant internal and external review and is one of the most comprehensive evaluations of toxicity of a chemical ever performed by the Agency. Following release of the report, the Office of Solid Waste and Emergency Response (OSWER) will participate in a cross-program review of the implications of the report for the regulation and management of dioxin by EPA. We anticipate that this review will culminate in OSWER guidance addressing the management of dioxin at CERCLA and RCRA sites.

The Office of Solid Waste and Emergency Response does not believe it is prudent to establish new, and possibly varying, precedents for Superfund or RCRA dioxin levels just prior to the release of this reassessment report. As with any other pollutant, it is important that EPA ensure appropriate national consistency in remediation efforts. The Agency has used 1 ppb as a residential cleanup level and between 5 ppb and 20 ppb as a commercial/industrial cleanup level at CERCLA and RCRA cleanup sites for dioxin in soil in the past; it is anticipated that OSWER will be issuing guidance, informed by the reassessment effort, that will provide a basis for the selection of dioxin cleanup levels in the near future. In the interim, for sites that require the establishment of a final dioxin soil cleanup level prior to the release of the reassessment report and

development of OSWER guidance, EPA should generally use 1 ppb (TEQs) as a starting point for residential soil cleanup levels for CERCLA non-time critical removal sites (time permitting, for emergency and time critical sites) and as a PRG for remedial sites. EPA should generally use a level within the range of 5 ppb to 20 ppb (TEQs) as a starting point for cleanup levels at CERCLA non-time critical removal sites (time permitting, for emergency and time critical sites) and as a PRG for remedial sites for commercial/industrial soil. These levels should also be used as starting points in setting soil cleanup levels at RCRA corrective action sites.

For CERCLA remedial sites, consistent with 40 CFR § 300.430(f)(5)(iii)(D), EPA should commit to reviewing Records of Decision (RODs) (i.e., RODs in which this Directive has been used to develop dioxin soil cleanup levels) promptly following the release and analysis of the reassessment report and OSWER guidance, and, if necessary, to making changes to the RODs and cleanup actions, based on the information contained in the reassessment report and in the OSWER guidance. Similarly, in the case of non-time critical removal actions (time permitting, for emergency and time critical actions), EPA should commit to reviewing Action Memoranda promptly following the release and analysis of the reassessment report and OSWER guidance, and, if necessary, to making changes to the Action Memoranda and cleanup actions, based on the information contained in the reassessment report and the OSWER guidance. EPA should similarly commit to reviewing RCRA cleanup decisions (i.e., decisions for which this Directive has been used) promptly following the release and analysis of the reassessment report and OSWER guidance.

IMPLEMENTATION

Regional management should consult with the appropriate Office of Emergency and Remedial Response (OERR) Regional Centers on all proposed Fund and Potentially Responsible Party-lead site decisions under CERCLA, including other Federal agency-lead and state-lead site decisions, involving the development of dioxin soil cleanup levels for non-time critical removal sites (time permitting, for emergency and time critical removal sites) and remedial sites. Consultation should be initiated at the risk assessment stage. For Federal agency-lead sites, OERR will, in turn, notify the Federal Facilities Restoration Reuse Office of ongoing consultations. The Office of Site Remediation Enforcement will provide support if enforcement issues are identified. For consultation procedures, refer to the OSWER "Headquarters Consultation for Dioxin Sites", 9200.4-19, December 13, 1996, plus the OSWER "Consolidated Guide to Consultation Procedures for Superfund Response Decisions", 9200.1-18FS, May 1997.

In the case of EPA-lead RCRA corrective action sites, Regions should provide the Office of Solid Waste Permits and State Programs Division (OSW/PSPD) with proposed dioxin soil cleanup levels (i.e., prior to notice and comment) in order to ensure appropriate implementation of this Directive. For state-lead RCRA corrective action sites, it is also recommended that states use the dioxin levels recommended by this Directive as starting points in setting soil cleanup levels. States are encouraged to share their approaches with the Regions in a manner consistent with established procedures for EPA support and oversight of state RCRA Corrective Action programs.

The levels in this Directive are recommended unless extenuating site-specific circumstances warrant different levels, a more stringent state applicable or relevant and appropriate requirement (ARAR) establishes a cleanup level at CERCLA sites, or a more stringent state requirement applies at RCRA sites. We recommend that levels other than 1 ppb (TEQs) for residential soils and outside the range of 5 ppb to 20 ppb (TEQs) for commercial/industrial soils be used only where evidence exists that risks posed by the site differ from risks estimated using standard national default guidance values. These recommendations apply to RCRA corrective actions, CERCLA non-time critical removal actions (time permitting, for emergency and time-critical actions) and CERCLA remedial actions where cleanup levels are to be developed for dioxin in soil, regardless of whether dioxin itself drives the decision-making process.

The recommended levels found in this Directive, generally considered protective of human health and the environment, apply to surface soils. Please note that with respect to human health, these levels are based on the direct contact exposure pathway. The recommended levels in this Directive do not apply to other exposure pathways, such as migration of soil contaminants to ground water or to agricultural products. While the focus of this Directive is on soils, these recommended levels also apply to sediments in the event that this environmental medium is considered to be a direct exposure pathway for human receptors.

This document provides guidance to EPA staff. The guidance is designed to communicate national policy on dioxin cleanups for soil. The document does not, however, substitute for EPA's statutes or regulations, nor is it a regulation itself. Thus, it cannot impose legally-binding requirements on EPA, states, or the regulated community, and may not apply to a particular situation based upon the circumstances. EPA may change this guidance in the future, as appropriate.

If you have any questions concerning this Directive, please contact either Marlene Berg at (703)603-8701 in Headquarters or Elmer Akin of Region 4 at (404)562-8634, as Marlene and Elmer are

co-chairs of the Superfund Dioxin Workgroup. For the RCRA Corrective Action program, please contact Robert Hall of the Office of Solid Waste Permits and State Programs Division at (703)308-8484. Attached, for your information, is a list of Regional points of contact who are serving on the dioxin workgroup.

Attachment: Superfund Dioxin Workgroup: Regional Points of Contact

cc: Mike Shapiro, OSWER
Peter Grevatt, OSWER
Steve Luftig, OERR
Elaine Davies, OERR
Larry Reed, OERR
Gershon Bergeisen, OERR
David Bennett, OERR
Bruce Means, OERR
Betsy Shaw, OERR
Paul Nadeau, OERR
Tom Sheckells OERR
Murray Newton, OERR
John Cunningham, OERR
Dave Evans, OERR
Joe LaFornara, OERR
Mark Mjoness, OERR
Jim Woolford, FFRRO
Elizabeth Cotsworth, OSW
Barry Breen, OSRE
Tudor Davies, OW
Craig Hooks, FFEO
Earl Salo, OGC
Bill Sanders, OPPT
Bill Farland, ORD
Regional Counsel, Regions I-X
Peggy Schwebke, Region 5
Superfund Dioxin Workgroup

EPA/ROD/R04-02/027
2002

EPA Superfund
Record of Decision:

BRUNSWICK WOOD PRESERVING
EPA ID: GAD981024466
OU 01
BRUNSWICK, GA
06/19/2002

RECORD OF DECISION

SUMMARY OF REMEDIAL ALTERNATIVE SELECTION
OPERABLE UNIT ONE

BRUNSWICK WOOD PRESERVING SITE

BRUNSWICK, GLYNN COUNTY, GEORGIA

PREPARED BY

U. S. ENVIRONMENTAL PROTECTION AGENCY

REGION 4

ATLANTA, GEORGIA

DECLARATION OF THE RECORD OF DECISION
OPERABLE UNIT ONE

SITE NAME AND LOCATION

Brunswick Wood Preserving Site
Brunswick, Glynn County, Georgia
EPA ID No. GAD981024466

STATEMENT OF BASIS AND PURPOSE

This decision document presents the Selected Remedy for Operable Unit One (OU1) of the Brunswick Wood Preserving Site located in Brunswick, Glynn County, Georgia. This remedy was chosen in accordance with the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA), as amended by the Superfund Amendments and Reauthorization Act of 1986 (SARA), 42 U. S. C. Section 9601 et seq., and to the extent practicable, the National Oil and Hazardous Substances Pollution Contingency Plan (NCP), 40 CFR Part 300. This decision is based on the administrative record for the Brunswick Wood Preserving Site.

The State of Georgia, as represented by the Georgia Environmental Protection Division, has been the support agency during the Remedial Investigation and Feasibility Study (RI/ FS) process for the Brunswick Wood Preserving Site. As such, they have reviewed the documents that comprise the RI/FS and have been involved in the process. The State concurs with the Selected Remedy.

ASSESSMENT OF THE SITE

The response action selected in this Record of Decision is necessary to protect the public health or welfare or the environment from actual or threatened releases of hazardous substances into the environment.

DESCRIPTION OF SELECTED REMEDY

Operable Unit One (OU1) will primarily address site- wide soils and groundwater to protect human health, while Operable Unit Two (OU2) will primarily address ecological risks posed to Burnett Creek and the surface water pathway, upon completion of the Baseline Ecological Risk Assessment (BERA). This remedial action for OU1 addresses both the remaining principal threats posed by this Site (site soils and sediments) and the contaminated groundwater beneath the Site. The OU1 remedial action for the soils/sediments and groundwater is ***Capping with Construction of Subsurface Barriers***. The major components of the selected remedy for this remedial action include:

- Construction of two caps over the IM-1/2 and IM-4/5 ponds, consisting of subcaps, geosynthetic liners, and a 2.5 foot thick soil layer.
- Construction of 3 to 5 foot thick subcaps under the caps. These caps will consist at a minimum of soils and sediments from three sources: the CCA Waste Cell, site soils above the performance standard of 1 ppb TEQ dioxin, and selected sediments from Burnett Creek located at Perry Lane Road and in the short east-west reach of the creek just south of Perry Lane Road.
- Solidification and/or stabilization of the subcap materials.
- Construction of subsurface barrier walls to contain groundwater, consisting of slurry-filled trenches to be dug to the weathered limestone located at 50 to 65 feet deep.
- In-situ groundwater treatment using chemical oxidation to enhance natural degradation of site contaminants in groundwater outside the cap/wall at IM-1/2.
- Long-term monitoring to ensure that the remedy is protective. This monitoring would include: sampling under the caps to see if natural processes break down site

contaminants, groundwater sampling outside the slurry walls, and ensuring the slurry walls' integrity.

- Engineering controls to control surface water runoff, dust, air quality, etc. and ensure that Remedial Action Objectives are met during and after putting the remedy in place.
- Institutional controls as necessary to restrict future land use and groundwater use.

STATUTORY DETERMINATIONS

The selected remedy for Operable Unit One (OU1) is protective of human health. Future remedial action will take place as necessary as part of OU2 to ensure protection of the environment, upon completion of the Baseline Ecological Risk Assessment. The selected remedy complies with Federal and State requirements that are legally applicable or relevant and appropriate to the remedial action, and is cost-effective. This remedy utilizes permanent solutions and alternative treatment technology, to the maximum extent practicable. The remedy set forth in this document satisfies the statutory preference for treatment as a principal element of the remedy for some of the site soils and sediments; however, the majority of the principal threats remaining at the Site are being left on-site without treatment. The rationale for not choosing alternative remedial actions that would completely satisfy this statutory preference is based upon technical feasibility, consideration of short-term risk to human health and the environment, and an extraordinarily high cost. Because this remedy will result in hazardous substances, pollutants, or contaminants remaining on-site above levels that allow for unlimited use and unrestricted exposure, a statutory review will be conducted within five years after initiation of remedial action to ensure that the remedy is, or will be, protective of human health.

ROD DATA CERTIFICATION CHECKLIST

The following information is included in the Record of Decision. Additional information can be found in the Administrative Record file for the Site.

- Chemicals of concern (COCs) and their respective concentrations.
- Baseline risk represented by the COCs.
- Cleanup levels established for COCs and the basis for the levels.
- How source materials constituting principal threats will be addressed.
- Current and reasonably anticipated future land use assumptions and current and potential future beneficial uses of groundwater used in the baseline risk assessment and the ROD.
- Potential land and groundwater use that will be available at the Site as a result of the Selected Remedy.
- Estimated capital, operation and maintenance (O&M), and total present worth costs; discount rate; and the number of years over which the remedy cost estimates are projected.
- Key factors that led to selecting the remedy.

AUTHORIZING SIGNATURE

19 JUN 02

RICHARD D. GREEN
DIRECTOR
WASTE MANAGEMENT DIVISION
U.S. EPA REGION 4

DATE

12.4.1 FUTURE LAND USE

The site is currently unused, but zoned for a commercial use. However, upon implementation of the soil/sediment portion of the selected remedy, it is possible that the Site soils could be available for a residential land use, for the reasons given in Section 12.2. Until such determination is made, institutional controls are anticipated to be part of the selected remedy so that future land use will be restricted to a commercial use. These controls may also restrict any future activity at the site that would compromise the effectiveness of the remedy.

An unrestricted land use would not be available until the groundwater cleanup standards are met outside the barrier walls and capped areas. It is anticipated that the groundwater cleanup standards can be met within a 30 year time frame, if not sooner. It is also anticipated that site development of the land could proceed prior to meeting the groundwater cleanup standards.

Achievement of the soil/sediment and groundwater performance standards will remove the potential for future impacts to Burnett Creek.

12.4.2 CLEANUP LEVELS

The purpose of this response action is to control risks posed by direct contact with soil and groundwater, and to minimize migration of contaminants from soils/ sediments to groundwater. The results of the baseline risk assessment indicate that existing site conditions pose an excess lifetime cancer risk to a future site worker of 7E-04, from direct contact with contaminated soils. The risk from site soils is primarily due to dioxin. The selected remedy shall address surface soils contaminated with dioxin in excess of 1 part per billion (ppb), as measured in human health toxicity equivalents to 2,3,7,8-TCDD, which is the most toxic of the dioxin/ furan congeners. The selected remedy will reduce the excess lifetime cancer risk to a future site worker to 3E-05, from exposure to site soils. Groundwater outside the slurry walls will be remediated until all drinking water standards have been met and attained for three consecutive years.

12.4.3 COMMUNITY AND ENVIRONMENTAL BENEFITS

The Site's value is enhanced by its proximity to both natural and anthropogenic features. Restoring this Site to a productive use will potentially restore economic benefits to the County that are currently being unrealized. Such restoration will also help revitalize the local community and will remove a potential source of urban blight. Environmental benefits will be realized by eliminating contaminated groundwater discharges to Burnett Creek, in addition to preventing direct contact of ecological receptors to contaminated sediments in the old creosote ponds on the site.

13.0 STATUTORY DETERMINATION

Under Section 121 of CERCLA, 42 U.S.C. § 9621, EPA must select remedies that are protective of human health and the environment, comply with applicable or relevant and appropriate requirements (unless a statutory waiver is justified), are cost effective, and utilize permanent solutions and alternative treatment technologies or resource recovery technologies to the maximum extent practicable. In addition, CERCLA includes a preference for remedies that employ treatment that permanently and significantly reduce the volume, toxicity, or mobility of hazardous wastes as their principal element. The following sections discuss how the selected remedy meets these statutory requirements.

13.1 PROTECTION OF HUMAN HEALTH AND THE ENVIRONMENT

The selected remedy provides protection of human health and the environment by: eliminating, reducing, and controlling risk through engineering controls and/ or institutional controls; and via soil/sediment and groundwater treatment as delineated

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C2 - Management of scientific committees; scientific co-operation and networks

Scientific Committee on Food

CS/CNTM/DIOXIN/20 final

OPINION

OF THE

SCIENTIFIC COMMITTEE ON FOOD

ON THE

RISK ASSESSMENT OF DIOXINS AND

DIOXIN-LIKE PCBS IN FOOD

UPDATE BASED ON NEW SCIENTIFIC INFORMATION AVAILABLE SINCE THE ADOPTION OF THE SCF OPINION OF 22ND NOVEMBER 2000

Adopted on 30 May 2001.

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Terms of Reference

The Committee is asked to consider whether there is a need to update its opinion on the risk assessment of dioxins and dioxin-like PCBs in food on the basis of new scientific information available since the release of the SCF opinion of 22nd November 2000.

Background

The Scientific Committee on Food (SCF) adopted its opinion on the risk assessment of dioxins and dioxin-like PCBs in food in November 2000 (SCF, 2000). In its derivation of the temporary tolerable weekly intake (t-TWI) of 7 WHO-TEQ/kg bw the Committee used a cluster of sensitive lowest observed adverse effect levels (LOAELs) for effects on the reproductive function and the immune system of the male offspring of rats administered a single gavage dose of 2,3,7,8-TCDD during gestation, a subtle effect on cognitive recognition in the offspring of rhesus monkeys fed a diet containing 2,3,7,8-TCDD for up to three years, and the development of endometriosis in the rhesus monkey dams from the same studies fed the diet for 42 months.

A key aspect of the assessment was the use of the "body burden approach" which the Committee used to scale doses across species. The Committee identified the limitations in the estimation of body burdens of the animals in the studies used, and consequently in the associated estimated human daily intakes (EHDI) of 2,3,7,8-TCDD derived from these studies. The Committee was unable to identify any single study as being sufficient, by itself, to provide a firm basis for the establishment of a tolerable intake. It therefore considered that these studies provided EHDIs in the range of 12.5 to 30 pg 2,3,7,8-TCDD/kg bw, and within the limits of precision of the estimates, all contributed to the derivation of a tolerable intake. Applying a 10-fold uncertainty factor to these EHDIs suggested a tolerable intake in the range 1 to 3 (rounded figures) pg 2,3,7,8-TCDD/kg bw per day. There were no scientific data to guide the Committee on selection of a single value from the range of 1 to 3 pg 2,3,7,8-TCDD/kg bw per day. However, because of the acknowledged uncertainties the Committee concluded that the lower end of the range, i.e. 1 pg/kg bw per day, should be considered as a temporary tolerable intake.

Since the adoption of the SCF opinion new scientific information on the toxicity of dioxins has been published, which might have removed some of the uncertainties in the previous opinion. In addition, the SCF took cognisance of comments received from the Swedish National Food Administration (2001), the Norwegian Food Control Authority (2001) and from some members of the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) of the European Commission. These comments mainly addressed the use of the rat and monkey studies for the derivation of the t-TWI, particularly in the light of the new information published since the SCF expressed its opinion.

Introduction

In its opinion of 22nd November 2000, the Committee identified a number of shortcomings in the available database with respect to bolus dosing and repeated administration, the consequent foetal and maternal body burdens, and the availability of LOAELs instead of no observed adverse effect levels (NOAELs) for the most sensitive endpoints. Since some of the new studies might affect the evaluation of the pivotal studies used in its previous risk assessment the Committee found it appropriate to revisit and update its assessment. In its updated assessment the Committee has considered other relevant new studies, some older studies, and additional information that were found useful for the interpretation of the new findings. The Committee also considered further details supplied by the authors of some of the studies discussed in the previous opinion.

Updated evaluation of the pivotal studies

Studies of developmental toxicity in rats

Effects on the reproductive system of male offspring

In its risk assessment of 2,3,7,8-TCDD the Committee used results from studies of the offspring of pregnant rats given a single, oral dose by gavage on gestation day (GD) 15 (effects on reproductive organs) or GD 14 (effects on the immune system). The most sensitive effects reported were accelerated eye opening and a non-significant decrease (25%) in ejaculated sperm counts in the male offspring following a maternal bolus dose of 50 ng 2,3,7,8-TCDD/kg bw on GD 15 in Long Evans rats (Gray *et al*, 1997a). In another study in Holzman rats using a similar protocol, Mably *et al.* (1992) found statistically significant decreases in epididymis and cauda epididymis weights, daily sperm production, and cauda epididymal sperm number in the male offspring after a maternal single gavage dose of 64 ng/kg bw, the lowest dose tested in that study. In these and other single dose gavage studies, an additional number of reproductive and developmental parameters were affected in a dose-related manner in the male offspring at higher dose levels, i.e. from 160 ng 2,3,7,8-TCDD/kg bw onwards. At a maternal dose of 200 ng 2,3,7,8-TCDD/kg bw or higher Gray *et al.* (1997b) found external malformations of the genitalia in the female offspring.

In order to estimate the maternal body burden in the pregnant rats of these studies the Committee used results from a study by Hurst *et al.* (2000a). The Committee reviewed this study in which ^{3}H-2,3,7,8-TCDD concentrations were measured in the tissues of pregnant Long Evans dams at GD 16 following administration by gavage at GD 15 of 50, 200, 800 or 10000 ng/kg bw, and the average maternal body burdens were reported to be 30.6 (60%), 97.4 (48%), 522.8 (65%) or 585.2 (59%) ng 2,3,7,8-TCDD/kg bw (percentage of dose), respectively. The corresponding average foetal body burdens at GD 16 were 5.3, 13.2, 39.1 and 55.7 ng 2,3,7,8-TCDD/kg bw. This study led the Committee to use a figure of 60% for the amount of 2,3,7,8-TCDD retained in pregnant rats

following a single gavage dose. On the other hand, the Committee used a figure of only 50% for the absorption of 2,3,7,8-TCDD from a dietary matrix. In support of this latter figure, the net absorption was found to be 50-55% when 2,3,7,8-TCDD was contained in normal rat and cows diets (Fries and Marrow, 1975; Jones *et al.*, 1989).

In its earlier discussion of the adequacy of using these single dose gavage studies for the risk assessment, the Committee had stressed that "The bioavailability of 2,3,7,8-TCDD to the foetus at a given maternal body burden may differ between a bolus dose (as in these rat studies) and dietary exposure at steady state. Intuitively, differences in foetal bioavailability would seem likely. Given that placental transfer will be mediated *via* the blood, it is serum rather than tissue levels that will be critical in determining the magnitude of foetal exposure. Following a bolus administration, serum 2,3,7,8-TCDD levels would be elevated before redistribution to the tissue compartments. In contrast, low-level chronic exposure will not significantly elevate serum levels. The time of dosing, GD 15, marks the onset of the endocrine-sensitive phase of sexual differentiation in rats and therefore represents a critical window for foetal exposure for these reproductive endpoints. (...) This would suggest that the critical determinant of these reproductive effects is the foetal concentration on GD 15, which, as noted above, is likely to be higher following a single bolus dose on this day than that resulting from lower level chronic exposure. This weakens the relevance to human dietary exposure." (SCF, 2000).

The issue of the difference in magnitude of the foetal body burden following an acute bolus dose compared to that resulting from a low level chronic exposure that leads to a similar maternal body burden now has been addressed in a new publication by Hurst *et al.* (2000b) who measured the radioactivity in both the maternal and foetal tissues of pregnant Long Evans dams at GD 9, 16, and 21 following subchronic administration of ^{3}H-2,3,7,8-TCDD. Female rats were dosed by gavage with 1, 10, or 30 ng of ^{3}H-2,3,7,8-TCDD/kg bw in corn oil, 5 days per week, for 13 weeks. At the end of this period, the rats were mated and dosing was continued every day throughout gestation (SCF 2000). The dosage regimen used produced a steady state of 2,3,7,8-TCDD in the dams. The average maternal and foetal body burdens at GD 16 are shown in Table 1 and compared with average maternal and foetal body burdens found at GD 16 following the single gavage administration of 2,3,7,8-TCDD on GD 15 in the previous study by Hurst *et al.* (2000a).

Table 1. Comparison of average maternal and foetal body burdens after single dose and subchronic 2,3,7,8-TCDD exposure to pregnant rats.

Single dose exposure at GD 15 [1]				Subchronic exposure [2]			
Single dose [3]	Body burden measured at GD 16			Adjusted daily dose [4]	Body burden measured at GD 16		
	Maternal [3]	Foetal [3]	Maternal/ Foetal		Maternal [3]	Foetal [3]	Maternal/ Foetal
50	30	5.3	5.7	0.71	20	1.4	14.3
200	97.4	13.2	7.4	7.1	120	7.5	16.0
800	523	39.1	13.4	21.3	300	15.2	20
1000	585	55.7	10.5				

[1] Data from Hurst *et al.* (2000a)
[2] Data from Hurst *et al.* (2000b)
[3] ng/kg bw
[4] ng/kg bw per day, adjusted to continuous exposure from 5 days/week

As expected, acute single gavage doses at GD 15 produced considerably higher foetal concentrations at GD 16 than subchronic administration of low daily doses leading to maternal steady state body burdens of similar magnitude. From Table 1 it appears that single gavage doses of 50 or 200 ng 2,3,7,8-TCDD/kg bw given at GD 15 produced foetal body burdens (5.3 or 13.2 ng/kg bw) at GD 16 that were 5.7 or 7.4 times lower than the corresponding maternal body burdens (30 or 97.4 ng/kg bw) whereas the foetal body burdens (1.4 or 7.5 ng/kg bw) obtained after subchronic administration of 0.71 or 7.1 ng 2,3,7,8-TCDD/kg bw per day were 14.3 or 16.0 times lower than the corresponding maternal steady state body burdens (20 or 120 ng/kg bw). The ratio of the maternal/foetal body burdens increased with increasing dose levels irrespective of the dosage regimen used.

The Committee noted that extrapolation of the relationship between the foetal and maternal body burdens using the data provided by Hurst *et al.* (2000a,b) did not intercept zero as would be expected since radiolabelled 2,3,7,8-TCDD had been used in both studies. The Committee therefore analysed the data and performed a best-fit analysis of each data set in the range of foetal body burdens from zero to 15.2 with the curves constrained to pass through the origin. It was found that both data sets could be fit to power equations (Annex I). The equations were used to calculate the corresponding acute and subchronic maternal body burdens for a number of foetal body burdens. From these calculations it was determined that the factor to convert maternal body burden following acute dosing into a corresponding steady state body burden is approximately 2.6 (Table 2).

It should be noted that these mathematical calculations of corresponding values for body burdens by no means provide assurance that the correct relationships have been found. Others could presumably be of equal validity. However, they were used solely to describe

the data as an aid to extrapolation between acute gavage dose studies and subchronic studies using daily doses for the purpose of estimating steady state body burdens.

Table 2. Calculated corresponding values of foetal, acute maternal and subchronic steady state maternal body burdens of 2,3,7,8-TCDD.

Foetal body burden (ng/kg bw)	Acute maternal body burden (ng/kg bw)	Subchronic (steady state) maternal body burden (ng/kg bw)	Ratio subchronic maternal/acute maternal body burden
1.2	5.0	12.3	2.5
1.4	5.9	14.6	2.5
1.7	7.5	18.6	2.5
1.8	8.0	20.0	2.5
1.9	8.5	21.0	2.5
2.1	10	25.0	2.5
3.0	15.5	39.0	2.5
5.3	31	78.6	2.5
6.3	38.5	99.0	2.6
7.5	47.5	122	2.6
8.0	52	134	2.6
9.0	60	156	2.6
13.2	95.7	251	2.6
15.2	113	299	2.7

Thus, a foetal body burden of 5.3 ng 2,3,7,8-TCDD/kg bw, which according to Hurst *et al.* (2000a) was associated with a maternal body burden of 31 ng/kg bw after a single bolus dose at the LOAEL of 50 ng/kg bw in the Long Evans rat in the study of Gray *et al.* (1997a), would correspond to a steady state maternal body burden of approximately 79 ng/kg bw. Similarly, the estimated maternal body burden of 38.5 ng/kg bw after the single gavage LOAEL dose of 64 ng/kg bw in the study by Mably *et al.* (1992) corresponds to a foetal body burden of 6.3 ng/kg bw which in turn would require a body burden of approximately 99 ng/kg bw at steady state (Table 2).

Hurst *et al.* (2000b) also discussed the study by Faqi *et al.* (1998) on the effects of low doses of 2,3,7,8-TCDD on the reproductive system of the male offspring of Wistar rats. In that study, the dams were treated subcutaneously prior to mating and throughout mating, pregnancy and lactation. They received an initial loading dose of 25, 60, or 300 ng ^{14}C-2,3,7,8-TCDD/kg bw 2 weeks prior to mating, followed by weekly maintenance doses of 5, 12, or 60 ng TCDD/kg bw. The size of the maintenance doses was based on a reported elimination half-life of 3 weeks for adult rats. For example, this means that at the low dose the initial loading dose would produce a maternal body burden of 25 ng 2,3,7,8-TCDD/kg bw which after one week had declined to 20 ng/kg bw but, following the weekly maintenance dose of 5 ng/kg bw, would again rise to 25 ng/kg bw. After birth, developmental landmarks in the male offspring were monitored. Effects on male

reproduction were studied on postnatal days (PND) 70 and 170. The number of sperm per cauda epididymis was reduced in all 2,3,7,8-TCDD treated groups at puberty and at adulthood. Daily sperm production was permanently decreased, as was the sperm transit rate in the 2,3,7,8-TCDD exposed male offspring, thus increasing the time required by the sperm to pass through the cauda epididymis. Moreover, the male offspring of the 2,3,7,8-TCDD groups showed an increased number of abnormal sperm when investigated at adulthood. Mounting and intromission latencies were significantly increased in the low and high dose groups, but not in the mid dose group. The Committee noted the lack of a clear dose-response relationship for most of these effects in the treated groups. In the high dose group, serum testosterone concentration was decreased at adulthood and permanent changes in the testicular tubuli included pyknotic nuclei and the occurrence of cell debris in the lumen. The fertility of the male offspring was not affected in any of the dosed groups. The intended (pseudo) steady state body burden at the LOAEL in this study using subcutaneous administrations was 25 ng 2,3,7,8-TCDD/kg bw which, according to Table 2, would correspond to a foetal body burden of 2.1 ng 2,3,7,8-TCDD/kg bw. However, the Committee noted that, following the dosage regimen of weekly maintenance doses that was used (see above), a maintenance dose of 5 ng/kg bw would have been given at GD 14 when the maternal body burden had declined to 20 ng/kg bw. According to Table 2, a maternal body burden of 20 ng/kg bw in equilibrium corresponds to a subchronic foetal body burden of 1.8 ng/kg bw. The additional acute dose of 5 ng/kg bw during this critical time period in gestation would produce an extra foetal body burden of 1.2 ng/kg bw, resulting in a total foetal body burden of 3.0 ng/kg bw. According to Table 2, a maternal body burden of 39 ng 2,3,7,8-TCDD/kg bw at steady state would be needed to produce this foetal body burden.

In a recent study by Ohsako *et al.* (2001) pregnant Holtzman rats were given a single oral dose of 0, 12.5, 50, 200 or 800 ng 2,3,7,8-TCDD/kg bw on GD 15, and the male offspring were examined on PND 49 or 120. In this study, there were no changes seen on testicular or epididymal weights nor in daily sperm production or sperm reserve at any of the doses used. However, the weight of the urogenital complex, including the ventral prostate, was significantly reduced at doses of 200 and 800 ng 2,3,7,8-TCDD/kg bw in rats sacrificed on PND 120. Moreover, the anogenital distance of male rats sacrificed on PND 120 showed a significant decrease in the groups receiving doses of 50 ng TCDD/kg or higher. TCDD administration resulted in no apparent dose-dependent changes in levels of either serum testosterone or luteinizing hormone. These results suggest that low-dose 2,3,7,8-TCDD administration had a greater effect on the development of the external genital organs and ventral prostate than on the development of the testis and other internal genital organs. Assuming that 60% of a single gavage dose was retained in the body at GD16 (Hurst *et al.*, 2000a), the NOAEL of 12.5 ng 2,3,7,8-TCDD/kg bw would result in a maternal body burden of 7.5 ng/kg bw. This would translate into a maternal body burden of 19 ng/kg bw at steady state following subchronic daily 2,3,7,8-TCDD administration. The LOAEL level of 50 ng 2,3,7,8-TCDD/kg bw corresponds to a maternal body burden of 31 ng/kg bw which would equate to a steady state maternal body burden of 79 ng 2,3,7,8-TCDD/kg bw (Table 2).

The Committee noted that, in the study of Ohsako *et al.* (2001), reverse transcription-polymerase chain reaction analysis revealed that, in the ventral prostates of the PND 49 group, 2,3,7,8-TCDD administration at all dose levels resulted in a dose-dependent increase in 5α-reductase type 2 mRNA level and decrease in androgen receptor mRNA level. These changes were not observed at PND 120 and were not associated with any adverse sequelae at the lowest dose of 12.5 ng 2,3,7,8-TCDD/kg bw. The authors suggested that the decrease in the size of the ventral prostate observed after maternal 2,3,7,8-TCDD exposure at 200 and 800 ng/kg bw might be due to decreased responsiveness of the prostate to androgen caused by an insufficient level of expression of androgen receptor during puberty.

In an earlier 3-generation reproduction study using Sprague-Dawley rats Murray *et al.* (1979) found that chronic dietary administration of 10 ng 2,3,7,8-TCDD/kg bw per day was a clear LOAEL in producing significantly decreased fertility in the F_1 and F_2 generations, but not in the F_0 generation. Other effects seen at that dose level included decreases in litter size at birth, gestation survival (proportion of pups born alive), and neonatal survival and growth. A daily dose of 100 ng 2,3,7,8-TCDD/kg bw produced significant decreases in fertility and neonatal survival in the F_0 generation which precluded continuation of this high dose level in subsequent generations. The lowest dose level used was 1 ng 2,3,7,8-TCDD/kg bw/day, which produced no significant or consistent effects and was considered a NOAEL. Nisbet and Paxton (1982) have pointed out that mild renal morphological changes and reduced pup survival were also seen in the low dose group, however these effects did not occur consistently across all generations. Cross-mating studies using untreated males and females mated with males and females of the 100 ng 2,3,7,8-TCDD/kg bw/day F_0 generation indicated that 2,3,7,8-TCDD affected the fertility of the females but not the fertility of the males. When simple first-order kinetics is used, assuming 50% absorption of 2,3,7,8-TCDD from the diet and an elimination half-life of 21 days in the rat, it can be calculated that the daily doses of 1 or 10 ng 2,3,7,8-TCDD used by Murray *et al.* (1979) would correspond to maternal body burdens at steady state of approximately 15 or 150 ng 2,3,7,8-TCDD/kg bw, respectively. The estimated foetal body burdens would be 1.4 and 8.8 ng 2,3,7,8-TCDD, respectively (Table 2). As judged from the results of the pivotal acute, single dose studies mentioned above such body burdens would not be expected to affect the fertility of the male offspring. However, it should be noted that the F_0 generation males were not exposed *in utero* and Murray *et al.* (1979) performed no cross-mating studies with animals of the F_1 and F_2 generations. More importantly, this study did not address the sensitive end-points included in the more recent studies. In view of this, and the relatively large margin between the body burdens associated with the NOAEL and the LOAEL (15 and 150 ng 2,3,7,8-TCDD/kg bw, respectively) the Committee did not include this study among the pivotal studies used in its previous assessment, nor in the current update.

Taken together, these studies provide evidence of adverse effects on the reproductive system in the male (and female) offspring of pregnant rats exposed to 2,3,7,8-TCDD. The studies demonstrate reduction in daily sperm production, cauda epididymal sperm number and epididymis weight as well as accelerated eye opening, reduction in anogenital

distance and feminised sexual behaviour in the male offspring associated with maternal steady state body burdens in the range of 39 – 99 ng 2,3,7,8-TCDD/kg bw. Reduction in weights of testes and size of sex-accessory glands, such as the ventral prostate in the male offspring, and development of external malformations of genitalia in female offspring as well as reduced male and/or female fertility require higher maternal body burdens. The Committee noted that the most sensitive end-points identified differed between studies. This might reflect strain differences in sensitivity and/or even minor differences in the experimental conditions, e.g. the diet (Ashby *et al.* 2000). The Committee also noted that in the study of Ohsako *et al.* (2001) a single maternal gavage dose of 12.5 ng 2,3,7,8-TCDD/kg bw produced a decrease in the androgen receptor mRNA level in the ventral prostate at puberty (PND 49), indicative of reduced androgenic responsiveness. However, at this dose level none of the above mentioned adverse effects were seen in the male offspring. This dose corresponds to an estimated maternal steady state body burden of approximately 19 ng 2,3,7,8-TCDD/kg bw. As with enzyme induction, altered expression of growth factors and enhanced oxidative stress, the Committee considered this effect to be either an early marker of exposure to 2,3,7,8-TCDD or an event induced in animals that may or may not result in adverse effects at higher body burdens.

Table 3 gives a summary of the NOAEL and LOAELs (rounded figures) for the most sensitive adverse effects of 2,3,7,8-TCDD on developmental endpoints in experimental animals.

TABLE 3. Estimated animal steady state body burdens of 2,3,7,8-TCDD and associated estimated human daily intakes (EHDI) at NOAEL and LOAELs in the pivotal studies

Study	Endpoint	NOAEL	LOAEL	Estimated maternal steady state body burden [1] (ng/kg bw)	Associated EHDI (pg/kg bw)
Mably *et al.*, 1992	**Holzman rats:** Decreased sperm count in male offspring		64 ng/kg bw single bolus dose by gavage	100 [2]	50
Gray *et al.*, 1997a	**Long Evans rats:** Accelerated eye opening and decreased sperm count in male offspring		50 ng/kg bw single bolus dose by gavage	80 [2]	40
Faqi *et al.*, 1998	**Wistar rats:** Decreased sperm production and altered sexual behavior in male offspring		Maintenance of 25 ng/kg bw by subcutaneous injections	40 [2]	20
Ohsako *et al.*, 2001	**Holzman rats:** Decreased anogenital distance in male offspring	12.5 ng/kg bw single bolus dose by gavage		20 [3]	10
			50 ng/kg bw single bolus dose by gavage	80 [3]	40

[1] Increment over background. Background body burden in rats is about 4 ng TEQ/kg bw (WHO, 2000).

[2] Composite value resulting from pseudo steady state body burden and acute body burden on GD 15.

[3] Maternal body burden at GD 16.

Effects on the immune system in the male offspring

In the study of Gehrs and Smialowicz (1999), used by the Committee in its previous assessment, a modest but significant suppression of delayed type hypersensitivity to bovine serum albumin was observed in the male offspring of pregnant F344 rats given a single oral gavage dose on GD 14 of 100 ng 2,3,7,8-TCDD/kg bw (the lowest dose tested). Higher doses (300, 1000 or 3000 ng 2,3,7,8-TCDD/kg bw) also produced changes

in the thymic T-cell phenotypes and thymus in the offspring. According to Table 2 an estimated maternal body burden of 60 ng 2,3,7,8-TCDD/kg bw following the acute exposure would result in a foetal body burden of 9.0 ng 2,3,7,8-TCDD/kg bw which in turn would require a steady state body burden of 156 ng 2,3,7,8-TCDD/kg bw after chronic exposure at a lower dose.

The Committee noted a new study by Nohara *et al.* (2000) in which pregnant Holtzman rats were given a single oral dose of 0, 12.5, 50, 200 or 800 ng 2,3,7,8-TCDD/kg bw on GD 15 and the thymus and spleen of male offspring were examined on PND 5, 21, 49 or 120. The weights of the thymus and spleen of the 2,3,7,8-TCDD exposed offspring did not differ from those of the control animals. In the thymus, dose dependent induction of CYP1A1 mRNA was observed on PND 5 following maternal exposure to 50 ng 2,3,7,8-TCDD/kg bw and higher. The induction gradually decreased on PND 21 and 49. There were no changes in cell number and cellular populations in the thymus at any time. In contrast, CYP1A1 mRNA induction in the spleen was very weak, but the numbers of splenocytes were decreased in a dose-dependent manner at puberty on PND 49, but not on PND 21 and 120. However, this decrease only reached significance at the 800 ng 2,3,7,8-TCDD/kg bw exposure level. No changes were detected in the mRNA levels for a number of cytokines in the spleen.

These studies demonstrate that the effects on the immune system of the male offspring of pregnant rat exposed to 2,3,7,8-TCDD occur only at higher doses than the effects seen on the reproductive organs and their function. Therefore, the Committee did not consider these studies pivotal to the updated assessment.

Studies in rhesus monkeys

The Committee, in its opinion of 22 November 2000, identified two studies of the effects of 2,3,7,8-TCDD administered to groups of female rhesus monkeys of one colony as providing a LOAEL of 0.15 ng/kg bw per day after prolonged dietary administration. These studies (Schantz and Bowman, 1989; Rier *et al.*, 1993) were included in the group of studies that was used in the Committee's determination of a tolerable intake for 2,3,7,8-TCDD. However, the Committee noted that it was not able to determine the clinical significance for humans, if any, of the findings of a subtle, non-persistent, neurobehavioural change in the offspring of the 2,3,7,8-TCDD treated monkeys in the first of the two studies (Schantz and Bowman, 1989). With regard to the findings of the second study (Rier *et al.*, 1993), the development of endometriosis in the rhesus monkeys some 10 years after the dietary treatment with 2,3,7,8-TCDD had been discontinued, the Committee identified some problems in the reporting and results. These were that it was not clear whether identical surgical procedures had been carried out on control and treated monkeys, that body weights had not been reported and that the colony had a very high incidence of endometriosis (SCF, 2000). The publication of two additional studies of these monkeys (Rier *et al.*, 2001a; Rier *et al.*, 2001b) supplemented by unpublished data (Rier, personal communication) has provided the opportunity for the Committee to review its opinion.

Estimates of intake of 2,3,7,8-TCDD

In its previous opinion (SCF, 2000) the Committee determined the body burden of 2,3,7,8-TCDD in rhesus monkeys resulting from intakes corresponding to the LOAEL using a published estimate of the daily intake of 2,3,7,8-TCDD by monkeys of the 5 ng/kg diet group (0.151 ng/kg bw per day; DeVito *et al.*, 1995). However, it was not possible to verify this estimate as not all the relevant information had been published. Additional information provided in a recent paper (Rier *et al.*, 2001a), supplemented by unpublished data (Rier, personal communication), has somewhat clarified the situation. It would thus appear that, in estimating the intake of 0.15 ng 2,3,7,8-TCDD/kg bw per day by the 5 ng/kg diet group, a value for the mean body weight of this group equivalent to the median body weight of the 25 ng/kg diet group had been used (DeVito *et al.*, 1995).

The original dietary consumption records have been used to estimate the cumulative intake of 2,3,7,8-TCDD by surviving individual animals of the 5 ng/kg diet group (Rier *et al.*, 2001b) and this data was provided to the Committee (Rier, personal communciation). However, the individual body weights to which these consumption figures relate are those measured when the animals were finally killed, not to their body weights during the period of administration of the 2,3,7,8-TCDD containing diets. It would appear that the mean body weight of the animals in the 5 ng 2,3,7,8-TCDD/kg diet group may have been greater than that of the 25 ng 2,3,7,8-TCDD/kg diet group. Therefore, depending on the assumptions used, the Committee could calculate intakes between 0.13 and 0.15 ng 2,3,7,8-TCDD/kg bw per day for this group of monkeys.

Endometriosis and serum levels of 2,3,7,8-TCDD analogues

In the first of the new papers, Rier and her colleagues (Rier *et al.*, 2001a) have recorded the serum concentrations of dioxin congeners measured in those rhesus monkeys that had been studied previously to determine the incidence and severity of endometriotic lesions. Of the original experimental groups of eight animals receiving 0, 5 or 25 ng of 2,3,7,8-TCDD/kg diet for periods of approximately 4 years, there were six survivors of each of the 0 and 5 ng/kg diet groups and three survivors of the 25 ng/kg group. Thirteen years after termination of the 2,3,7,8-TCDD exposure samples of blood were collected for determination of the concentrations of 2,3,7,8-TCDD congeners and the incidence and severity of endometriosis was reassessed. It is stated that the diagnostic severity of endometriosis in the animals was similar on both occasions.

Serum samples were analysed for six chlorinated dibenzo-*p*-dioxins, ten chlorinated dibenzofurans and four chlorinated biphenyls. The mean concentrations of four congeners (2,3,7,8-TCDD, 1,2,3,6,7,8-hexachlorodibenzofuran [1,2,3,6,7,8-HxCDF], 3,3',4,4'-tetrachlorobiphenyl [TCB] and 3,3',4,4',5-pentachlorobiphenyl [PeCB]) in the serum of monkeys that had been treated with 2,3,7,8-TCDD were found to be statistically significantly higher than those of the control group of monkeys. There was a significant correlation of the total administered dose of 2,3,7,8-TCDD (dosing completed some 13 years previously) with the serum concentration of 2,3,7,8-TCDD. In addition, both these

parameters correlated with the serum concentrations of 1,2,3,6,7,8-HxCDF and PeCB whereas only the cumulative dose of 2,3,7,8-TCDD correlated with the serum concentrations of TCB.

Increased serum concentrations of 2,3,7,8-TCDD and 1,2,3,6,7,8-HxCDF were not associated with the presence of endometriosis in the monkeys, whereas the concentrations of both the TCB and PeCB congeners were increased in animals with the disease that had been treated with 2,3,7,8-TCDD. This paper has provided additional information that addresses some of the problems that the Committee had identified with the original study of the endometriosis occurring in monkeys administered 2,3,7,8-TCDD in the diet. It is recorded that similar surgical procedures, biopsy or laparoscopy, had been carried out on animals of both the treated and control groups. In addition, it has been reported that having been subjected to one or more laparoscopies is not a risk factor for the development of endometriosis in the rhesus monkey (Hadfield *et al.*, 1997). Therefore, the use of these procedures does not constitute a bias in the original study of Rier *et al.* (1993).

The new results indicating an association of endometriosis with increased concentrations of polychlorinated biphenyl compounds (PCBs) has, however, raised a number of new questions. Several hypotheses to explain the observations were considered by the Committee. These hypotheses were that:

- the association of increased serum concentrations of PCBs with endometriosis reflects a causal relationship independent of the prior treatment with 2,3,7,8-TCDD;
- the association is fortuitous and the administration of 2,3,7,8-TCDD has either initiated or promoted the development of endometriosis;
- the accumulation of dioxin congeners represents a biomarker of exposure to 2,3,7,8-TCDD;
- the accumulation of dioxin congeners represents a biomarker of an effect of 2,3,7,8-TCDD.

Since there is no evidence that the accumulation of the dioxin congeners and dioxin-like PCBs had occurred prior to the development of endometriosis the Committee considered that the available data were inadequate to determine whether any one of these hypotheses was more probable than any other. Particular points considered by the Committee and other relevant information are detailed in Annex 2.

Due to the uncertainties raised by the new findings, the Committee had less confidence in the quantitative relationship between exposure to 2,3,7,8-TCDD and the incidence of endometriosis in monkeys. It therefore decided not to include Rier *et al.* (1993) as a pivotal study in the updated assessment, though it recognized that effects were reported at body burdens similar to those calculated for other (rat) studies.

Neurobehavioural effects in the offspring of 2,3,7,8-TCDD treated rhesus monkeys

Neither of the papers of Rier and colleagues (2001a, 2001b) provides new information that would affect the opinion of the Committee with regard to the neurobehavioural development study of the offspring (Schantz and Bowman, 1989). In view of the doubts expressed earlier by the Committee on the significance of the neurobehavioural observations (SCF, 2000), and the firmer basis for extrapolation from the pivotal rodent studies that is now available, the Committee decided not to include the study of Schantz and Bowman (1989) as a pivotal study in the updated assessment.

Immune function and serum levels of 2,3,7,8-TCDD analogues

The second new study by Rier and her colleagues (Rier *et al.*, 2001b) investigated the effects of 2,3,7,8-TCDD exposure on the immune system of rhesus monkeys as manifested in the phenotype and function of peripheral blood mononuclear cells (PBMC). Clinical studies have indicated a relationship between endometriosis and deficiencies in humoral and cell-mediated immunity.

Samples of blood were taken from the surviving animals from the original study (Rier *et al.*, 1993) and from twelve additional, similarly-aged animals with no exposure to 2,3,7,8-TCDD or polyhalogenated aromatic hydrocarbons. The phenotype of the PBMC was measured by flow cytometric analysis after staining with monoclonal antibodies specific to various human (and rhesus monkey) surface cell antigens. The secretion of the cytokines, tumour necrosis factor-α (TNF-α), interferon-γ and interleukins 6 and 10, by PBMC in response to stimulation by phytohaemagglutinin (PHA) or polyinosinic acid-polycytidylic acid (PIC) was measured. The cytolytic activity of PBMC was measured by ^{51}Cr release from two target cell lines (Rier *et al.*, 2001b).

In the study of the phenotype of PBMC no significant differences between 2,3,7,8-TCDD exposed and unexposed animals are recorded, though all 18 animals that had not been exposed to 2,3,7,8-TCDD were included in the control group. However, it is noted that, when the results from only the animals of the original study (Rier *et al.*, 1993) were considered, there was a significant increase in the numbers of CD16+/CD56+ natural killer cells in the 2,3,7,8-TCDD-treated animals.

Cytokine production by the PBMC in response to PHA or PIC was observed to differ significantly between control monkeys and those exposed to 2,3,7,8-TCDD only for release of TNF-α in response to PHA. Within group differences in terms of the responses to PHA and PIC were recorded for two other cytokines. Varied numbers of animals from the combined control group were included in this study. Significant correlations between PHA-induced TNF-α production and serum concentrations of 2,3,7,8-TCDD, 1,2,3,6,7,8-HxCDD, and PeCB, but notably not TCB, and also with serum triglycerides (Rier *et al.*, 2001a), were recorded when the data only from animals of the original experiment (Rier *et al.*, 1993) were analysed.

The lytic activity of rhesus monkey PBMC against RAJI (but not K562) cells exhibited a non-significant trend to decreased activity with increased group dietary concentration of 2,3,7,8-TCDD (Rier *et al.*, 1993). If, for individual animals, the results of the assay were plotted against cumulative dose of 2,3,7,8-TCDD this trend became significant.

The associations of effects on immune parameters with serum concentrations of 2,3,7,8-TCDD and some dioxin-like analogues (Rier *et al.*, 2001b) are consistent with prior observations of the immunotoxicity of 2,3,7,8-TCDD in many animal species and also with the possible involvement of TNF-α in the toxicity of 2,3,7,8-TCDD. However, the inclusion of additional 'control' animals in parts of this study, prospective to the study itself but retrospective to the original dietary administration of 2,3,7,8-TCDD, renders the study of little value to toxicological evaluation. The Committee considered that it was not possible to establish causality of immune system changes in rhesus monkeys receiving 2,3,7,8-TCDD in the diet and therefore did not include this study as a pivotal study in the updated assessment.

Derivation of a tolerable intake of 2,3,7,8-TCDD and related compounds for humans

Based on previously existing and additional uncertainties regarding the monkey studies, the Committee decided to base its updated assessment on the rodent studies rather than on the rodent and monkey studies. The above discussion has identified the pivotal studies, which provide a NOAEL and LOAELs for the most sensitive effects of 2,3,7,8-TCDD exposure in experimental animals, i.e. developmental effects in rat male offspring. The Committee has calculated that sensitive responses (LOAELs) were associated with steady state body burdens between 40 and 100 ng 2,3,7,8-TCDD/kg bw with associated estimated human daily intakes (EHDI) in the range of 20 - 50 pg 2,3,7,8-TCDD/kg bw (see Table 3). For the NOAEL as observed in the study of Ohsako *et al.* (2001) a maternal steady state body burden of 20 ng/kg bw and an associated EHDI of 10 pg 2,3,7,8-TCDD/kg bw was calculated.

In deriving a tolerable intake for 2,3,7,8-TCDD the Committee considered the associated EHDIs based on both the NOAEL and the LOAELs.

Tolerable intake

In order to arrive at a tolerable intake of 2,3,7,8-TCDD for humans an uncertainty factor needs to be applied. In the case of using the EHDI of 10 pg/kg bw based on a NOAEL the uncertainty factor should account for the possible differences between experimental animals and humans in susceptibility (toxicokinetics and toxicodynamics) to 2,3,7,8-TCDD and the potential interindividual variation in susceptibility (toxicokinetics and toxicodynamics) to 2,3,7,8-TCDD within the human population.

- The use of an uncertainty factor to account for differences between experimental animals and humans in toxicokinetics was not required since the default toxicokinetic

factor was replaced by actual data in calculating the body burdens used to scale doses across species.

- To account for interindividual variations in humans in toxicokinetics (i.e. absorption, biotransformation, accumulation and elimination of 2,3,7,8-TCDD) an uncertainty factor has to be applied. In considering aspects of the variability in the toxicokinetic properties of 2,3,7,8-TCDD in humans, the Committee noted that reported mean half-lives of 2,3,7,8-TCDD in man vary from 5.1 to 11.3 years (IARC, 1997). The Committee noted that the human data were primarily derived from occupationally exposed men. The distribution of these mean half-lives shows a mean of 8 years and a standard deviation of 2.1 years. Using the mean plus two standard deviations (12.2 years) to describe the 95% upper interval for the half-life of 2,3,7,8-TCDD in humans, a data-derived uncertainty factor of 1.5 (12.1/8) would be predicted for interindividual variations in toxicokinetics. However, the variability in toxicokinetics among females may not be adequately covered and the most sensitive effects of 2,3,7,8-TCDD were seen after 2,3,7,8-TCDD exposure of female animals. Because the Committee had no structured and useful information on the potential variations among women as regards the most important determinants in toxicokinetics, which are size of body fat stores, CYP1A2 concentrations in liver, and rate of metabolism of 2,3,7,8-TCDD, the Committee found it most appropriate to use the default uncertainty factor of 3.2 as recommended by WHO (WHO, 1994) to account for interindividual variations with regard to absorption, biotransformation, accumulation and elimination of 2,3,7,8-TCDD within the human population.

- With regard to the potential differences in toxicodynamics between experimental animals and humans and within the human population, studies of Ah receptor binding affinity and adverse responses directly dependent on Ah receptor activation suggest that humans are less sensitive to 2,3,7,8-TCDD than responsive rodent strains. However, studies of some biochemical or cellular effects, such as CYP1A1 and CYP1A2 induction, suggest a comparable sensitivity. Therefore, for some endpoints it can not be excluded that the most sensitive humans might be as sensitive to the adverse effects of 2,3,7,8-TCDD as experimental animals. The Committee concluded that no uncertainty factor needs to be applied for differences in toxicodynamics between experimental animals and humans and for interindividual variation among humans.

Therefore, the Committee considered an uncertainty factor of 3.2 applied to a NOAEL adequate for the protection of human health from exposure to 2,3,7,8-TCDD.

Applying this 3.2-fold uncertainty factor to the EHDI of 10 pg 2,3,7,8-TCDD/kg bw, calculated from the NOAEL in the Ohsako study, a tolerable intake of 3 pg/kg bw per day can be derived.

In using the LOAEL instead of the NOAEL an additional uncertainty factor needs to be applied. As the LOAELs reported for the sensitive endpoints were considered to be close to the NOAELs and were representing marginal effects, the Committee found it appropriate to allow a factor of 3 to account for the use of LOAELs instead of NOAELs. In this case, this leads to an overall uncertainty factor of 9.6 (3 x 3.2).

Applying this 9.6-fold overall uncertainty factor to the EHDI of 20 pg/kg bw calculated from the LOAEL in the study of Faqi *et al.* (1998) a tolerable intake of 2 pg/kg bw per day can be derived. Using a similar approach to the LOAELs in the other studies in Table 3 would result in the figures of 4 and 5 pg/kg bw per day for the tolerable intake.

The Committee recognized that the Wistar rats as used in the study by Faqi *et al.* (1998) might be the most sensitive rat strain. The Committee therefore concluded that 2 pg/kg bw per day should be considered as a tolerable intake for 2,3,7,8-TCDD.

Recognizing that compounds like 2,3,7,8-TCDD and related substances have very long half-lives in the human body, the Committee considered that the tolerable intake should be expressed on a weekly rather than a daily basis. Therefore the Committee established a tolerable weekly intake (TWI) of 14 pg 2,3,7,8-TCDD/kg bw.

In recognising that the other 2,3,7,8-substituted PCDDs, PCDFs and the dioxin-like PCBs have a similar mode of action as 2,3,7,8-TCDD, the Committee, as in its previous opinion, concluded that the TWI for 2,3,7,8-TCDD should be extended to include all 2,3,7,8-substituted PCDDs and PCDFs, and the dioxin-like PCBs, expressed as WHO TEQ (van den Berg *et al.* 1998) and established a group TWI of 14 pg WHO TEQ/kg bw for these compounds.

Because the new studies provided a firm basis for the evaluation of the pivotal rat studies the Committee removed the designation "temporary" from the TWI.

Although the Committee has now established a TWI of 14 pg WHO-TEQ/kg bw, it wishes to stress that, given the average dietary intakes of dioxins and dioxin-like PCBs in the European countries of 1.2 – 3.0 pg/kg bw per day, a considerable proportion of the European population would still exceed the TWI derived by the Committee.

The Committee therefore concluded that the considerations set out in the chapters on risk characterisation, risk management strategies and recommendations of the previous assessment of November 2000 were still valid.

Annex I

Establishment of a relationship between foetal 2,3,7,8-TCDD body burdens and maternal body burdens in pregnant rats at GD16 following either a single gavage dose on GD15 or following preceding subchronic low dose administration leading to steady state.

The critical determinant of the reproductive effects seen in the male offspring of pregnant rats given a single gavage dose of 2,3,7,8-TCDD on GD 15 is the foetal concentration on GD 15/GD 16, which is likely to be higher following a single bolus dose on this day than that resulting from lower level chronic exposure. Therefore, information is needed to compare maternal body burdens from either acute or chronic exposure that produce similar foetal concentrations. Studies by Hurst *et al.* (2000 a,b) provide a basis for this comparison (Table 1).

In the first study by Hurst *et al.* (2000a) in which ^{3}H-2,3,7,8-TCDD concentrations were measured in the tissues of pregnant Long Evans dams at GD 16 following administration by gavage at GD 15 of 0.05, 0.2, 0.8 or 1.0 μg/kg bw, the average maternal body burdens were reported to be 30.6 (60%), 97.4 (48%), 522.8 (65%) or 585.2 (59%) ng 2,3,7,8-TCDD/kg bw (percentage of dose), respectively. The corresponding average foetal body burdens at GD16 were 5.3, 13.2, 39.1 and 55.7 ng 2,3,7,8-TCDD/kg bw.

In the second study by Hurst *et al.* (2000b) the radioactivity was measured in both the maternal and foetal tissues of pregnant Long Evans dams at GD 16 following subchronic administration of ^{3}H-2,3,7,8-TCDD. Female rats were dosed by gavage with 1, 10, or 30 ng of ^{3}H-2,3,7,8-TCDD/kg bw in corn oil, 5 days per week, for 13 weeks. At the end of this period, the rats were mated and dosing was continued every day throughout gestation. The dosage regimen used produced a steady state of 2,3,7,8-TCDD in the dams. The average maternal and foetal body burdens at GD 16 are shown in Table a and compared with the average maternal and foetal body burdens found at GD 16 following the single gavage administration of 2,3,7,8-TCDD on GD 15 in the previous study by Hurst *et al.* (2000a).

Table a. Comparison of average maternal and foetal body burdens after single dose and subchronic 2,3,7,8-TCDD exposure to pregnant rats.

Single dose exposure at GD15[1)]				Subchronic exposure [2)]			
Single dose [3)]	Body burden measured at GD 16			Adjusted daily dose [4)]	Body burden measured at GD 16		
	Maternal [3)]	Foetal [3)]	Maternal/ Foetal		Maternal [3)]	Foetal [3)]	Maternal/ Foetal
50	30	5.3	5.7	0.71	20	1.4	14.3
200	97.4	13.2	7.4	7.1	120	7.5	16.0
800	523	39.1	13.4	21.3	300	15.2	20
1000	585	55.7	10.5				

[1)] Data from Hurst *et al.* (2000a)
[2)] Data from Hurst *et al.* (2000b)
[3)] ng/kg bw
[4)] ng/kg bw per day, adjusted to continuous exposure from 5 days/week

The Committee noted that linear extrapolation of the relationship between the foetal and maternal body burdens using the data provided by Hurst *et al.* (2000a,b) did not intercept zero as would be expected since radiolabelled 2,3,7,8-TCDD was used in both studies. The Committee therefore performed a best-fit analysis of each data set within the dose ranges of interest for the risk assessment, constraining the curves to pass through the origin.

The data from the acute study (Hurst *et al.*, 2000a) were treated in the following way: The two highest values were considered to be outside the dose range of interest for the assessment. Initially, the highest figure was taken out, and the data were fitted to a number of possible functions using SigmaPlot. It was found that the data were best fit to a power equation. Using SigmaPlot, corresponding values between foetal body burdens and maternal body burdens were generated. The Committee found that an estimated body burden of 112.5 ng 2,3,7,8-TCDD/kg bw would correspond to a foetal body burden of 15.2 ng 2,3,7,8-TCDD/kg bw and used this figure in its final calculation (Table b).

The data from the study of maternal and foetal concentration of 2,3,7,8-TCDD following subchronic administration leading to steady state were used as derived by Hurst *et al.* (2000 b) (Table a).

Table b. Comparison of average maternal and foetal body burdens after single dose and subchronic 2,3,7,8-TCDD exposure to pregnant rats.

Single dose exposure at GD15 [1]				Subchronic exposure [2]			
Single dose [3]	BBBody burden measured at GD 16			Adjusted daily dose [4]	BBBody burden measured at GD 16		
	Maternal [3]	Foetal [3]			Maternal [3]	Foetal [3]	
0	0	0		0	0	0	
50	30	5.3		0.71	20	1.4	
200	97.4	13.2		7.1	120	7.5	
-	112.5[5]	15.2		21.3	300	15.2	

[1] Data from Hurst *et al.* (2000a)
[2] Data from Hurst *et al.* (2000b)
[3] ng/kg bw
[4] ng/kg bw per day, adjusted to continuous exposure from 5 days/week
[5] Estimated figure

These two data sets were fit to power equations with the following result.

I. Acute study: $Y = 3.8791 \times X^{1.2418}$ ($R^2 = 0.999$) (Hurst *et al.* 2000a)

II. Subchronic study: $Y = 9.4843 \times X^{1,2685}$ ($R^2 = 0.999$) (Hurst *et al.* 2000b)

Where Y is the maternal body burden (ng 2,3,7,8-TCDD/kg bw) and X is the foetal body burden (ng 2,3,7,8-TCDD/kg bw).

These two equations were used to calculate the corresponding acute and subchronic maternal body burdens for a number of foetal body burdens ranging from 0 to 15.2 ng 2,3,7,8-TCDD/kg bw (Table c).

Table c. Corresponding values of foetal, acute maternal and subchronic steady state maternal body burdens of 2,3,7,8-TCDD.

Foetal body burden (ng/kg bw)	Acute maternal body burden (ng/kg bw)	Subchronic (steady state) maternal body burden (ng/kg bw)	Ratio subchronic maternal/acute maternal body burden
1.2	5.0	12.3	2.5
1.4	5.9	14.6	2.5
1.7	7.5	18.6	2.5
1.8	8.0	20.0	2.5
1.9	8.5	21.0	2.5
2.1	10	25.0	2.5
3.0	15.5	39.0	2.5
5.3	31	78.6	2.5
6.3	38.5	99.0	2.6
7.5	47.5	122	2.6
8.0	52	134	2.6
9.0	60	156	2.6
13.2	95.7	251	2.6
15.2	113	299	2.7

Annex II

Studies of endometriosis in rhesus monkeys - additional considerations

The Committee noted that the additional information available to it had resolved some of the matters that had been noted in its opinion of November 2000 (SCF, 2000). The high incidence (33%) of endometriosis in the colony noted previously (Rier *et al.*, 1993) was, in that paper, compared with an incidence of 27% noted in control animals of a study of radiation-induced endometriosis (Fanton and Golden, 1991). This information removed one of the reservations that the Committee had expressed previously. However, as mentioned above, the new results indicating an association of endometriosis with the increased concentrations of polychlorinated biphenyl compounds (PCBs) raised new questions. These are discussed in more detail here.

The original report of endometriosis in 2,3,7,8-TCDD-exposed rhesus monkeys was the result of adventitious observations that initiated a more detailed study (Rier *et al.*, 1993). The additional results reported in the recent paper (Rier *et al.*, 2001a) are also adventitious and the association of endometriosis with the increased concentrations of PCBs requires further evidence if it is to be accepted as causal.

The main problem with the recent study is that any possible exposure to PCBs is completely undefined. It has been recorded that seven samples of feed for these monkeys during the initial four years 2,3,7,8-TCDD feeding trial were analysed and found to contain 7.6 ± 2 µg/kg of total PCBs and 1.0 ± 0.2 µg/kg of DDE, means ± s.e., analytical technique not specified (Schantz and Bowman, 1989). Both control and 2,3,7,8-TCDD treated monkey chow were analysed (Rier *et al.*, 2001a). From the PCB levels found it can be calculated that the monkeys received approximately 0.2 µg total PCB/kg bw perday (assumptions: daily intake of chow 190 g; weight of monkeys 7.5 kg). Otherwise, only the results of the recent analyses provide evidence of exposure to PCBs.

An additional problem relates to the properties of one of the PCBs that was analysed. The TCB congener has been the subject of a comparative study of its clearance from the bodies of rhesus monkeys and rats (Abdel-Hamid *et al.*, 1981). Three female rhesus monkeys were administered an intravenous dose of ^{14}C-labelled TCB and held in metabolism cages for a period of 42 days. It was noted that 50% of the radioactivity was excreted within 14 days. However, recovery of the radioactivity was only 73% and it was suggested that, if the unrecovered material had been in the faeces, 50% of the dose could have been excreted in the first 8-10 days of the study. The residual radioactivity in the animals was predominantly in the adipose tissue, containing 2.3% of dose, more than twice that of all other tissues combined. Metabolites of TCB comprised more than 97% of the radioactivity in the faeces and, after 1 or 2 days, more than 50% of the radioactivity circulating in the blood was in the form of TCB metabolites. Therefore, if the half-life ($t_{½}$) of TCB in the rhesus monkeys of Rier and colleagues (2001a) is in the range of 1-14 days it can be estimated that a steady state body burden of 230 ng TCB/kg bw (lipid base; mean value for 2,3,7,8-TCDD exposed monkeys in the study) would be achieved by a

daily dietary intake of 3.4 or 48 ng TCB/kg bw, assuming $t_{½}$ of 14 or 1 days, respectively. Assumptions made are that the fat content of the rhesus monkey bodies is 15% and that the absorption of TCB from the gastrointestinal tract is 50%.
This body burden could be achieved within a period of less than 3 months provided the monkeys had the above-mentioned daily intake of TCB. However, most of the TCB circulating in the blood would be in the form of metabolites and not the parent compound that was analysed in the study of Rier *et al.* (2001a). On the other hand, in the absence of any TCB exposure no measurable amounts of TCB would be expected within less than 3 months. It is therefore not possible to attribute the endometriosis observed three years previously to exposure to PCBs with any certainty.

Several hypotheses have been offered to explain the observations. These can be summarised as followed:

- the association of increased serum concentrations of PCBs with endometriosis reflects a causal relationship independent of the prior treatment with 2,3,7,8-TCDD;
- the association is fortuitous and the administration of 2,3,7,8-TCDD has either initiated or promoted the development of endometriosis;
- the accumulation of dioxin congeners represents a biomarker of exposure to 2,3,7,8-TCDD;
- the accumulation of dioxin congeners represents a biomarker of an effect of 2,3,7,8-TCDD.

Not all of these possible hypotheses are mutually exclusive and most of them have been explicitly suggested as being possible by Rier and her colleagues (Rier *et al.*, 2001a). It is necessary to consider alternative options in turn.

A comparison of the first two options reveals that there are distinct differences.

Firstly, the treatment of the monkeys with 2,3,7,8-TCDD was undertaken in circumstances in which the dose and its period of administration were clearly defined; there is nothing that defines any dose or duration of exposure to PCB isomers.

Secondly, both the incidence and severity of the endometriosis as assessed earlier (Rier *et al.*, 1993) exhibited a dose-response relationship with 2,3,7,8-TCDD within the limitations of the use of only two treated groups in the original study.

Thirdly, there is an association of serum TCB concentrations with development of endometriosis in the absence of known exposure to PCBs. Three out of a group of four Pb-treated monkeys had endometriosis and the mean concentration of TCB in the serum of the group was elevated (Rier *et al.*, 2001a). This indicates a lack of specificity of association of endometriosis with exposure to PCBs.

Fourthly, there is a temporal association of 2,3,7,8-TCDD exposure with development of endometriosis, which cannot be shown to exist for any association with PCB isomers.

Fifthly, the relationship between incidence and severity of endometriosis and PCB exposure was studied in female rhesus monkeys; despite initial observations suggesting an association (Arnold *et al.*, 1990), the results of the final study did not support any relationship (Arnold *et al.*, 1996). In that study, groups of 20 female rhesus monkeys received 0, 5, 20, 40 or 80 µg Aroclor 1254/kg bw per day for 6 years in a toxicological-reproduction study. The incidence of endometriosis in the control group was 37% (6/16 animals) and 25% (16/64) in the exposed groups. The PCB mixture used contained 0.05% TCB (and 0.01% PeCB) (Arnold *et al.* 1990). Thus the monkeys were exposed to 0, 2.5, 10, 20, or 40 ng TCB/kg bw per day. Interestingly, Arnold *et al.* (1996) report that the PCB mixture used contained polychlorinated dibenzofurans and dioxin-like PCBs equivalent to 182 µg TCDD equivalents/g Aroclor 1254. Therefore the monkeys in this study received 0, 0.91, 3.64, 7.28 or 14.56 ng TCDD equivalents/kg bw per day for 6 years without any increase in incidence and severity of endometriosis being noted. The method used to calculate 2,3,7,8-TCDD equivalents was not stated.

Finally, there are studies of the promotion by 2,3,7,8-TCDD, in mice and rat, of the growth of surgically induced endometriotic cysts, although at higher doses than in these monkeys (SCF 2000). In addition, the promotion by 2,3,7,8-TCDD of the growth and survival of autotransplanted endometrial tissue in the abdomens of cynomolgus monkeys has been observed by Yang *et al.* (2000). Female cynomolgus monkeys (5-6 per group) were orally dosed with 2,3,7,8-TCDD-containing gelatin capsules, 5 days per week for 12 months following the surgical auto-implantation of endometrial strips into multiple abdominal sites. Average delivered TCDD doses were 0, 0.71, 3.57 or 17.86 ng/kg bw per day. Significantly greater numbers of the endometrial strips survived in the two highest TCDD dose groups at necropsy compared to the controls (26.7% and 33.3% vs. 16.0%, respectively). The size of the implants increased only in the high dose group. It is noteworthy that surviving endometrial strips actually regressed in size in the lowest TCDD dose group. Serum concentrations of the cytokine IL-6 were significantly decreased while levels of IL-6 sR (soluble receptor) were increased in the high dose monkeys at termination. These studies provide evidence supportive of a causal relationship between 2,3,7,8-TCDD exposure and the development of endometriosis.

These differences are consistent with there being an association of 2,3,7,8-TCDD, rather than PCBs, with development of endometriosis in rhesus monkeys.

The third hypothesis, that the presence of dioxin congeners represents a biomarker of exposure to 2,3,7,8-TCDD, assumes that contamination of the solution of 2,3,7,8-TCDD during preparation of diets resulted in the PCB congeners being incorporated in the diet and retained in the tissues of the rhesus monkeys (Rier *et al.*, 2001a). This is implausible given the short half-life of TCB in the rhesus monkey and the time that had elapsed since dosing was terminated.

The fourth hypothesis, that the accumulation of TCB is a consequence of exposure to 2,3,7,8-TCDD and therefore a biomarker of effect, has been discussed by Rier and

colleagues (2001a). However, they note that it might be expected that treatment with 2,3,7,8-TCDD would be expected to increase the metabolism and excretion of TCB.

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Food and Agriculture Organization of the United Nations

World Health Organization

Joint FAO/WHO Expert Committee on Food Additives
Fifty-seventh meeting
Rome, 5-14 June 2001

SUMMARY AND CONCLUSIONS

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 5 to 14 June 2001. The purpose of the meeting was to evaluate certain food additives and contaminants.

Mrs. I. Meyland, Senior Scientific Adviser, Danish Veterinary and Food Administration, Søborg, Denmark, served as chairman and Professor R. Walker, Emeritus Professor of Food Science, School of Biological Sciences, University of Surrey, Guildford, Surrey, United Kingdom, served as vice-chairman.

Dr J.L. Herrman, International Programme on Chemical Safety, World Health Organization and Dr. Manfred Luetzow, Food Quality and Standards Service, Food and Nutrition Division, Food and Agriculture Organization of the United Nations, served as joint secretaries.

The present meeting was the fifty-seventh in a series of similar meetings. The tasks before the Committee were (a) to elaborate further principles for evaluating the safety of food additives and contaminants; (b) to assess certain food additives, flavouring agents, and contaminants; and (c) review and prepare specifications for selected food additives.

The report of the meeting will appear in the WHO Technical Report Series. Its presentation will be similar to that of previous reports, namely, general considerations, comments on specific substances, and recommendations for future work. An annex will include detailed tables (similar to the tables in this report) summarizing the main conclusions of the Committee in terms of acceptable daily intakes (ADIs) and other toxicological recommendations. Information on specifications for the identity and purity of certain food additives examined by the Committee will also be included.

The participants in the meeting are listed in Annex 1. Further information required or desired is listed in Annex 2. Items of a general nature that contain information that the Committee would like to disseminate quickly are included in Annex 3. Draft report items on the contaminants that were evaluated are included in Annex 4.

Toxicological monographs or monograph addenda on most of the substances that were considered will be published in WHO Food Additives Series No. 48.

Specifications for the identity and purity of the compounds listed in Annex 2 marked as N; N,T; R; or R,T will be published in FAO Food and Nutrition Paper Series 52, Addendum 9. Specifications for substances marked as S and S,T have been published previously in that series. However, if these specifications have not been adopted as Codex Advisory Specifications, they will be re-published in FAO Food and Nutrition Paper Series No. 52, Addendum 9.

Corrected version (corrections are on pages 6 and 16)

Acceptable daily intakes (ADIs), other recommendations, and information on specifications

1. Food additives evaluated toxicologically

Food additive	Specifications[a]	Acceptable daily intake (ADI) and other toxicological recommendations
Emulsifiers		
Diacetyltartaric and fatty acid esters of glycerol	R	0-50 mg/kg bw (temporary)[b]
Tartaric, acetic and fatty acid esters of glycerol, mixed	W[c]	ADI withdrawn[c]
Quillaia extracts	R, T[b]	0-5 mg/kg bw (temporary)[b]
Enzyme preparation		
Invertase from *Saccharomyces cerevisiae*	N	Acceptable[d]
Food colours		
ß-Carotene from *Blakeslea trispora*	N,T[b]	0-5 mg/kg bw (group ADI with synthetic ß-carotene)
Curcumin	R	0-1 mg/kg bw (temporary)[b]
Food salts		
Calcium dihydrogen diphosphate	N	} Included in the maximum tolerable daily intake of 70 mg/kg bw for phosphates, diphosphates, and polyphosphates
Monomagnesium phosphate	N,T[b]	
Sodium calcium polyphosphate	N	
Trisodium diphosphate	N,T[b]	
Glazing agent		
Hydrogenated poly-1-decene	R	0-6 mg/kg bw
Preservative		
Natamycin (pimaricin)	N,T[b]	0-0.3 mg/kg bw
Sweetening agent		
D-Tagatose	S	0-80 mg/kg bw
Thickening agents		
Carrageenan	R	} ADI "not specified"[e] (group ADI for carrageenan and processed *Eucheuma* seaweed)
Processed *Eucheuma* seaweed	R	
Curdlan	R	ADI "not specified"[e]
Miscellaneous substances		
Acetylated oxidized starch	N, R[f]	ADI "not specified"[e]
α-Cyclodextrin	N	ADI "not specified"[e]
Sodium sulfate	S	ADI "not specified"[e]

[a]N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new, or revised specifications are tentative and new information is needed; W, existing specifications withdrawn.

[b]See Annex 2.

[c]The ADI was withdrawn because the specifications for tartaric, acetic and fatty acid esters of glycerol, mixed, were combined with those of diacetyltartaric and fatty acid esters of glycerol under the latter name at the fifty-first meeting (WHO Technical Report Series, No. 891, 2000).

[d]Invertase from *Saccharomyces cerevisiae* that meets the specifications developed at the present meeting was considered to be acceptable because *S. cerevisiae* is commonly used in the preparation of food. Its use should be limited by Good Manufacturing Practice.

[e]ADI "not specified" is used to refer to a food substance of very low toxicity which, on the basis of the available data (chemical, biochemical, toxicological and other) and the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effects and from its acceptable background levels in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of

an ADI expressed in numerical form is not deemed necessary. An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e. it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal food of inferior quality or adulterated food, and it should not create a nutritional imbalance.

[f] The new specifications for Acetylated Oxidized Starch were integrated into the revised specifications for Modified Starches.

2. Food additives considered for specifications only

Food Additive	Specification[a]	Food Additive	Specification[a]
Acesulfame K (potassium salt)	R	Pectins	R
Blackcurrant extract	R	Smoked flavourings	R
Oxystearin	W	Tagetes extract	R
DL-Malic Acid	R[b]		

[a] N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new, or revised specifications are tentative and new information is needed; W, existing specifications withdrawn.

[b] The "call for data" asked for information on L-malic acid. However, no information about the uses of L-malic acid, other than its well-established use as a flavouring agent was received. As DL- and L-malic acid are different compounds made by different manufacturing processes, the specifications for DL-malic acid were corrected, and the reference to the specifications for L-malic acid were removed.

3. Revision of heavy metals limits for food additives

At its fifty-fifth meeting, the Committee began its implementation of a systematic five-year programme to replace the outdated test for heavy metals (as lead) in all existing food additive specifications with appropriate limits for individual metals of concern. Proposed lead and arsenic limits for 43 emulsifiers were established. As no alternative proposals were received by the deadline for submission of data for the present meeting, the new proposed limits were adopted, replacing those published in FAO Food and Nutrition Paper 52 and its addenda 1 to 7.

The second group of substances, considered at the present meeting, included 10 anticaking agents, 17 flavour enhancers, 10 sweetening agents, and 13 thickening agents. In response to the call for data, proposed limits and supporting data were received for sodium ferrocyanide.

The proposed changes to the current limits were as follows

- Limits for arsenic were deleted except for ferrocyanides of calcium, potassium and sodium, for which a limit of 3 mg/kg was proposed.
- Proposed limits for lead for the thickening agents and magnesium oxide were 2 mg/kg, for flavour enhancers and sweeteners 1 mg/kg, for phosphates 4 mg/kg, and for silicate anticaking agents 5 mg/kg.
- No limits were proposed for cadmium or mercury, as there were not concerns for their presence in any of the substances under review.
- Limits for heavy metals (as lead) were deleted.

Comments on the Committee's new proposed limits are invited. If alternative values and supporting data are not received by the deadline for submission of data for the fifty-ninth meeting, the proposed metal limits will be adopted and supersede the existing limits, replacing those published in FAO Food and Nutrition Paper 52 and its addenda 1 to 8.

Category	Food additive	INS	Sub	As	Pb	Hg	Cd	Other elements
Anticaking agent	Aluminium silicate	0559		-	5	-	-	
Anticaking agent	Calcium aluminium silicate	0556		-	5	-	-	F<50
Anticaking agent	Calcium silicate	0552		-	5	-	-	F<50
Anticaking agent	Ferrocyanides of Ca, K & Na	0538		3	5	-	-	Cu<10, Zn<25
Anticaking agent	Magnesium oxide	0530		-	2	-	-	
Anticaking agent	Magnesium silicates (synthetic)	0553	a	-	5	-	-	F<10
Anticaking agent	Silicon dioxide (amorphous)	0551		-	5	-	-	
Anticaking agent	Sodium aluminosilicate	0554		-	5	-	-	
Anticaking agent	Tricalcium phosphate	0341	iii	-	4	-	-	F<50
Anticaking agent	Trimagnesium phosphate	0342	iii	-	4	-	-	F<5
Flavour enhancer	Calcium-5'-guanylate	0629		-	1			
Flavour enhancer	Calcium 5'-inosinate	0633		-	1			
Flavour enhancer	Calcium 5'-ribonucleotides	0634		-	1	-	-	
Flavour enhancer	Calcium di-L-glutamate	0623		-	1	-	-	
Flavour enhancer	Dipotassium-5'-guanylate	0628		-	1	-	-	
Flavour enhancer	Dipotassium-5'-inosinate	0632		-	1	-	-	
Flavour enhancer	Disodium-5'-guanylate	0627		-	1	-	-	
Flavour enhancer	Disodium-5'-inosinate	0631		-	1	-	-	
Flavour enhancer	Disodium-5'-ribonucleotides	0635		-	1	-	-	
Flavour enhancer	Ethyl maltol	0637		-	1	-	-	
Flavour enhancer	L-Glutamic acid	0620		-	1	-	-	
Flavour enhancer	5'-Guanylic acid	0626		-	1	-	-	
Flavour enhancer	5'-Inosinic acid	0630		-	1	-	-	
Flavour enhancer	Magnesium di-L-glutamate	0625		-	1	-	-	
Flavour enhancer	Monoammonium L-glutamate	0624		-	1	-	-	
Flavour enhancer	Monopotassium L-glutamate	0622		-	1	-	-	
Flavour enhancer	Monosodium L-glutamate	0621		-	1	-	-	
Sweetening agent	Alitame	0956		-	1	-	-	
Sweetening agent	Aspartame	0951		-	1	-	-	
Sweetening agent	Cyclohexylsulfamic acid	0952		-	1	-	-	Se<30
Sweetening agent	Isomalt	0953		-	1	-	-	Ni<2
Sweetening agent	Lactitol	0966		-	1	-	-	Ni<2
Sweetening agent	Mannitol	0421		-	1	-	-	Ni<2
Sweetening agent	Saccharin and its Na, K and Ca salts	0954		-	1	-	-	Se<30
Sweetening agent	Sorbitol/ sorbitol syrup	0420		-	1	-	-	Ni<2
Sweetening agent	Sucralose	0955		-	1	-	-	
Sweetening agent	Xylitol	0967		-	1	-	-	Ni<2
Thickening agent	Ammonium alginate	0403		-	2	-	-	
Thickening agent	Ethyl cellulose	0462		-	2	-	-	
Thickening agent	Gum ghatti	0419		-	2	-	-	
Thickening agent	Hydroxypropyl cellulose	0463		-	2	-	-	
Thickening agent	Hydroxypropylmethyl cellulose	0464		-	2	-	-	
Thickening agent	Karaya gum	0416		-	2	-	-	
Thickening agent	Konjac flour	0425		-	2	-	-	
Thickening agent	Methylethyl cellulose	0465		-	2	-	-	
Thickening agent	Methyl cellulose	0461		-	2	-	-	
Thickening agent	Polyvinylpyrrollidone	1201		-	2	-	-	
Thickening agent	Powdered cellulose	0460	(ii)	-	2	-	-	
Thickening agent	Tara gum	0417		-	2	-	-	
Thickening agent	Tragacanth gum	0413		-	2	-	-	

4. Flavouring agents evaluated using the Procedure for the Safety Evaluation of Flavouring Agents

A. Pyrazine derivatives

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
2-Methylpyrazine	761	N	
2-Ethylpyrazine	762	N	
Propylpyrazine	763	N	
Isopropylpyrazine	764	N	
2,3-Dimethylpyrazine	765	N	
2,5-Dimethylpyrazine	766	N	
2,6-Dimethylpyrazine	767	N	
2-Ethyl-3-methylpyrazine	768	N	
2-Ethyl-6-methylpyrazine	769	N	
2-Ethyl-5-methylpyrazine	770	N	
2,3-Diethylpyrazine	771	N	
2-Methyl-5-isopropylpyrazine	772	N	
2-Isobutyl-3-methylpyrazine	773	N	
2,3,5-Trimethylpyrazine	774	N	
2-Ethyl-3,(5 or 6)-dimethylpyrazine	775	N	
3-Ethyl-2,6-dimethylpyrazine	776	N	
2,3-Diethyl-5-methylpyrazine	777	N	
2,5-Diethyl-3-methylpyrazine	778	N	
3,5-Diethyl-2-methylpyrazine	779	N	
2,3,5,6-Tetramethylpyrazine	780	N	
5-Methyl-6,7-dihydro-5H-cyclopentapyrazine	781	N	= No safety concern
6,7-Dihydro-2,3-dimethyl-5*H*-cyclopentapyrazine	782	N	
2-Isobutyl-3-methoxypyrazine	792	N	
Acetylpyrazine	784	N	
2-Acetyl-3-methylpyrazine	950	N	
2-Acetyl-3-ethylpyrazine	785	N	
2-Acetyl-3,(5 or 6)-dimethylpyrazine	786	N	
Methoxypyrazine	787	N	
(2,5 or 6)-Methoxy-3-methylpyrazine	788	N	
2-Ethyl(or methyl)-(3,5 or 6)-methoxypyrazine	789	N	
2-Methoxy-(3,5 or 6)-isopropylpyrazine	790	N	
2-Methoxy-3-(1-methylpropyl)-pyrazine	791	N	
(Cyclohexylmethyl)pyrazine	783	N	
2-Methyl-3,5 or 6-ethoxypyrazine	793	N	
2-(Mercaptomethyl)pyrazine	794	N	
2-Pyrazinylethanethiol	795	N	
Pyrazinylmethyl methyl sulfide	796	N	
(3,5 or 6)-(Methylthio)-2-methylpyrazine	797	N	
5-Methylquinoxaline	798	N	
Pyrazine	951	N	
5,6,7,8-Tetrahydroquinoxaline	952	N	

[a]N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new, or revised specifications are tentative and new information is needed; W, existing specifications withdrawn.

B. Aromatic substituted secondary alcohols, ketones and related esters

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
α-Methylbenzyl alcohol	799	N	No safety concern
α-Methylbenzyl formate	800	N	
α-Methylbenzyl acetate	801	N	
α-Methylbenzyl propionate	802	N	
α-Methylbenzyl butyrate	803	N	
α-Methylbenzyl isobutyrate	804	N	
p, α-Dimethylbenzyl alcohol	805	N	
Acetophenone	806	N	
4-Methylacetophenone	807	N	
p-Isopropylacetophenone	808	N	
2,4-Dimethylacetophenone	809	N	
Acetanisole	810	N	
1-(*p*-Methoxyphenyl)-2-propanone	813	N	
α-Methylphenethyl butyrate	814	N	
4-Phenyl-2-butanol	815	N	
4-Phenyl-2-butyl acetate	816	N	
4-(*p*-Tolyl)-2-butanone	817	N, T	
4-(*p*-Methoxyphenyl)-2-butanone	818	N	
4-Phenyl-3-buten-2-ol	819	N	
4-Phenyl-3-buten-2-one	820	N	
3-Methyl-4-phenyl-3-buten-2-one	821	N	
1-Phenyl-1-propanol	822	N	
α-Ethylbenzyl butyrate	823	N	
Propiophenone	824	N	
α-Propylphenethyl alcohol	825	N	
1-(*p*-Methoxyphenyl)-1-penten-3-one	826	N	
Ethyl benzoylacetate	834	N	
Ethyl 2-acetyl-3-phenylpropionate	835	N	
4-Acetyl-6-*t*-butyl-1,1-dimethylindan	812	N	Additional data required*
α-Isobutylphenethyl alcohol	827	N	No safety concern
4-Methyl-1-phenyl-2-pentanone	828	N	
1-(4-Methoxyphenyl)-4-methyl-1-penten-3-one	829	N	
3-Benzyl-4-heptanone	830	N	
1-Phenyl-1,2-propanedione	833	N	
Methyl β-naphthyl ketone	811	N	
Benzophenone	831	N	
1,3-Diphenyl-2-propanone	832	N	
Benzoin	836	N	

[a]N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new, or revised specifications are tentative and new information is needed; W, existing specifications withdrawn.

*Corrected from the earlier version, where this was given as "no safety concern".

C. *Benzyl derivatives*

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
Benzyl alcohol	025	R	= No safety concern
Benzyl formate	841	N	
Benzyl acetate	023	R	
Benzyl propionate	842	N	
Benzyl butyrate	843	N	
Benzyl isobutyrate	844	N	
Benzyl isovalerate	845	N	
Benzyl *trans*-2-methyl-2-butenoate	846	N	
Benzyl 2,3-dimethylcrotonate	847	N, T	
Benzyl acetoacetate	848	N	
Benzyl benzoate	024	R	
Benzyl phenylacetate	849	N	
Benzaldehyde	022	R	
Benzaldehyde dimethyl acetal	837	N	
Benzaldehyde glyceryl acetal	838	N	
Benzaldehyde propylene glycol acetal	839	N	
Benzoic acid	850	N	Evaluation not finalized[b]
Methyl benzoate	851	N	= No safety concern
Ethyl benzoate	852	N	
Propyl benzoate	853	N	
Hexyl benzoate	854	N	
Isopropyl benzoate	855	N	
Isobutyl benzoate	856	N	
Isoamyl benzoate	857	N	
cis-3-Hexenyl benzoate	858	N	
Linalyl benzoate	859	N	
Geranyl benzoate	860	N	
Glyceryl tribenzoate	861	N, T	Evaluations not finalized[b]
Propylene glycol dibenzoate	862	N, T	
Methylbenzyl acetate (mixed *o,m,p*)	863	N	= No safety concern
p-Isopropylbenzyl alcohol	864	N	
4-Ethylbenzaldehyde	865	N	
Tolualdehydes (mixed *o,m,p*)	866	N, T	
Tolualdehyde glyceryl acetal	867	N	
Cuminaldehyde	868	N	
2,4-Dimethylbenzaldehyde	869	N	
Benzyl 2-methoxyethyl acetal	840	N	

[a]N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new, or revised specifications are tentative and new information is needed; W, existing specifications withdrawn.

[b]Further information is required to determine whether this substance is in current use as a flavouring agent.

D. *Hydroxy- and alkoxy-substituted benzyl derivatives*

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
4-Hydroxybenzyl alcohol	955	-[b]	= No safety concern
4-Hydroxybenzaldehyde	956	-[b]	
4-Hydroxybenzoic acid	957	-[b]	
2-Hydroxybenzoic acid	958	-[b]	
Butyl-*p*-hydroxybenzoate	870	N, T	Evaluation not finalized[c]
Anisyl alcohol	871	N	= No safety concern
Anisyl formate	872	N, T	
Anisyl acetate	873	N	
Anisyl propionate	874	N	
Anisyl butyrate	875	N	
Anisyl phenylacetate	876	N	
Veratraldehyde	877	N	
p-Methoxybenzaldehyde	878	N	
p-Ethoxybenzaldehyde	879	N	
Methyl *o*-methoxybenzoate	880	N	
2-Methoxybenzoic acid	881	N	
3-Methoxybenzoic acid	882	N	
4-Methoxybenzoic acid	883	N	
Methyl anisate	884	N	
Ethyl *p*-anisate	885	N	
Vanillyl alcohol	886	N	
Vanillin	889	N	
4-Hydroxy3-methoxybenzoic acid	959	-[b]	
Vanillin acetate	890	N	
Vanillin isobutyrate	891	N	
Salicylaldehyde	897	N	
2-Hydroxy-4-methylbenzaldehyde	898	N	
Methyl salicylate	899	N	
Ethyl salicylate	900	N	
Butyl salicylate	901	N	
Isobutyl salicylate	902	N	
Isoamyl salicylate	903	N	
Benzyl salicylate	904	N	
Phenethyl salicylate	905	N	
o-Tolyl salicylate	907	N	
2,4-Dihydroxybenzoic acid	908	N	
Vanillyl ethyl ether	887	N	
Vanillyl butyl ether	888	N	
Ethyl vanillin	893	N	
Vanillin *erythro*- & *threo*-butan-2,3-diol acetal	960	-[b]	
Ethyl vanillin isobutyrate	953	N	
Ethyl vanillin propylene glycol acetal	954	N, T	
Piperonyl acetate	894	N	
Piperonyl isobutyrate	895	N	
Piperonal	896	N	
Ethyl vanillin β-d-glucopyranoside	892	N	

[a]N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new, or revised specifications are tentative and new information is needed; W, existing specifications withdrawn.

[b]Specifications will be considered at the fifty-ninth meeting of the Committee.

[c]Further information is required to determine whether this substance is in current use as a flavouring agent

E. *Aliphatic acyclic diols, triols, and related agents*

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
Glycerol	909	N, T	Evaluation not finalized[b]
3-Oxohexanoic acid glyceride	910	N, T	= No safety concern
3-Oxooctanoic acid glyceride	911	N, T	
Heptanal glyceryl acetal (mixed 1,2 and 1,3 acetals)	912	N	
1,2,3-tris[(1'-Ethoxy)ethoxy]propane	913	N	
3-Oxodecanoic acid glyceride	914	N, T	= Evaluations not finalized[b]
3-Oxododecanoic acid glyceride	915	N, T	
3-Oxotetradecanoic acid glyceride	916	N, T	
3-Oxohexadecanoic acid glyceride	917	N, T	
Glycerol monostearate	918	N, T	
Glyceryl monooleate	919	N, T	
Triacetin	920	N, T	
Glyceryl tripropionate	921	N, T	
Tributyrin	922	N, T	
Glycerol 5-hydroxydecanoate	923	N, T	
Glycerol 5-hydroxydodecanoate	924	N, T	
Propylene glycol	925	N, T	
Propylene glycol stearate	926	N, T	
1,2-di[(1-Ethoxy)ethoxy]propane	927	N	= No safety concern
4-Methyl-2-pentyl-1,3-dioxolane	928	N	
2,2,4-Trimethyl-1,3-oxacyclopentane	929	N	
Lactic acid	930	N	
Ethyl lactate	931	N	
Butyl lactate	932	N	
Potassium 2-(1'-ethoxy)ethoxypropanoate	933	N	
cis-3-Hexenyl lactate	934	N	
Butyl butyryllactate	935	N	
Pyruvic acid	936	N	
Pyruvaldehyde	937	N, T	
Ethyl pyruvate	938	N	
Isoamyl pyruvate	939	N	

[a]N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new, or revised specifications are tentative and new information is needed; W, existing specifications withdrawn.

[b]Further information is required to determine whether this substance is in current use as a flavouring agent.

F. *Aliphatic acyclic acetals*

Flavouring agent	No.	Specifications[a]	Conclusions based on current intake
1,1-Dimethoxyethane	940	N	= No safety concern
Acetal	941	N	
Heptanal dimethyl acetal	947	N	
4-Heptenal diethyl acetal	949	N	
Octanal dimethyl acetal	942	N	
2,6-Nonadienal diethyl acetal	946	N	
Decanal dimethyl acetal	945	N	
Citral dimethyl acetal	944	N	
Citral diethyl acetal	948	N	
Acetaldehyde ethyl *cis*-3-hexenyl acetal	943	N, T	

[a]N, new specifications prepared; R, existing specifications revised; S, specifications exist, revision not considered or required; T, the existing, new, or revised specifications are tentative and new information is needed; W, existing specifications withdrawn.

G. *Flavouring agents considered for specifications only*

No.	Flavouring agent	Specifications[a]	No.	Flavouring agent	Specifications[a]
10	Allyl tiglate	R	461	3-(Methylthio)propanol	R
12	Allyl cyclohexane acetate	R	478	3-(Methylthio)propyl acetate	R
14	Allyl cyclohexane butyrate	R	490	Allyl thiopropionate	R,T
15	Allyl cyclohexane valerate	R	510	2-Propanethiol	R
16	Allyl cyclohexane hexanoate	R	531	2-Naphthalenethiol	R
51	Isoamyl 2-methylbutyrate	R	543	Trithioacetone	R
58	Geranyl acetate	R	562	2,5-Dimethyl-2,5-dihydroxy-1,4-dithiane	R
64	Rhodinyl propionate	R	580	2-Methyl-2-(methyldithio)propanal	R
70	Geranyl hexanoate	R	581	Ethyl 2-(methyldithio)propionate	R
72	Geranyl isobutyrate	R	591	Methyl 2-oxo-3-methylpentanoate	R
74	Rhodinyl isobutyrate	R	599	Geranyl acetoacetate	R
77	Rhodinyl isovalerate	R	609	1,4-Nonanediol diacetate	R,T
78	3,7-Dimethyl-2,6-octadien-1-yl 2-ethylbutanoate	R	627	Aconitic acid	R,T
111	Lauric acid	R,T	642	3-Phenylpropyl hexanoate	R,T
113	Myristic acid	R,T	645	3-Phenylpropionaldehyde	R
115	Palmitic acid	R,T	648	Cinnamaldehyde ethylene glycol acetal	R
116	Stearic acid	R,T	652	Cinnamyl butyrate	R
172	Isobutyl heptanoate	R	656	Cinnamaldehyde	R
178	Nonyl octanoate	R	660	Propyl cinnamate	R
182	Isoamyl laurate	R,T	663	Butyl cinnamate	R
184	Butyl stearate	R	666	Heptyl cinnamate	R
191	trans-3-Heptenyl 2-methyl propanoate	R	671	Phenethyl cinnamate	R
240	omega-6-Hexadecenlactone	S	672	3-Phenylpropyl cinnamate	R
249	cis-4-Hydroxy-6-dodecenoic acid lactone	R	673	Cinnamyl cinnamate	R
260	2-Methylpentanal	R	676	alpha-Amylcinnamyl formate	R
270	2-Methyloctanal	R	677	alpha-Amylcinnamyl acetate	R
273	2,6-Dimethyloctanal	R	678	alpha-Amylcinnamyl isovalerate	R,T

No.	Flavouring agent	Specifi-cations[a]	No.	Flavouring agent	Specifi-cations[a]
304	Isopropyl formate	R	681	alpha-Amylcinnamaldehyde dimethyl acetal	R
306	Isopropyl propionate	R	698	o-Tolyl acetate	R
308	Isopropyl hexanoate	R	711	p-Vinylphenol	R
334	Methyl 3-hexenoate	R	719	Guaiacyl phenylacetate	R
344	Butyl 10-undecenoate	R	720	Hydroquinone monoethyl ether	R
347	2-Methyl-3-pentenoic acid	R	723	4-Ethyl-2,6-dimethoxyphenol	R
348	2,6-Dimethyl-6-hepten-1-ol	R	724	4-Propyl-2,6-dimethoxyphenol	R
350	Ethyl 2-methyl-3-pentenoate	R	726	4-Allyl-2,6-dimethoxyphenol	R
352	Hexyl 2-methyl-3&4-pentenoate (mixture)	R	729	Dihydroxyacetophenone	R,T
367	Terpinyl formate	R	732	Vanillylidene acetone	R
370	Terpinyl butyrate	R	740	Furfuryl propionate	R
372	Terpinyl isovalerate	R	741	Furfuryl pentanoate	R
374	p-Menth-8-en-1-ol	R	742	Furfuryl octanoate	R
390	gamma-Ionone	R,T	743	Furfuryl 3-methylbutanoate	R
416	5-Hydroxy-4-octanone	R	748	Amyl 2-furoate	R
424	2-Hydroxy-2-cyclohexen-1-one	R	749	Hexyl 2-furoate	R
428	d-Neo-Menthol	R	750	Octyl 2-furoate	R
434	p-Menth-1-en-3-ol	R	752	2-Phenyl-3-carbethoxyfuran	R,T
440	2-Ethyl-1,3,3-trimethyl-2-norbornanol	R	759	Furfuryl butyrate	R
442	Methyl 1-acetoxycyclohexyl ketone	R	760	Cinnamyl benzoate	R
457	(1-Buten-1-yl) methyl sulfide	R			

[a]R, existing specifications revised; S, specifications exist, revision not required; T, the existing, new, or revised specifications are tentative and new information is required.

4. Contaminants

Contaminant	Tolerable intake and other toxicological recommendations
3-Chloro-1,2-propanediol	PMTDI (provisional maximum tolerable daily intake): 2 µg/kg bw[a]
1,3-Dichloro-2-propanol	Establishment of a tolerable intake was considered to be inappropriate because of the nature of toxicity (tumorogenic in various organs in rats and the contaminant can interact with chromosomes and/or DNA); The Committee noted that the dose that caused tumours in rats (19 mg/kg bw per day) was about 20 000 times the highest estimated intake of 1,3-dichloro-2-propanol by consumers of soya sauce (1 µg/kg bw per day).[a]
Polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (PCBs)	PTMI (provisional tolerable monthly intake): 70 pg/kg bw[a]

[a]See Annex 4 for detailed information on the evaluation.

Annex 1

Fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives Rome, 5-14 June 2001

Members

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Annex 2

Further information required or desired

β-Carotene from Blakeslea trispora

Information is required on the method of analysis for residual solvents (ethyl acetate and isobutyl acetate). This information is required for evaluation in 2003.

Curcumin

The results of a reproductive toxicity study on a substance complying with the specifications for curcumin, known to be in progress, is required for evaluation in 2003.

Diacetyltartaric and fatty acid esters of glycerol

The following information relating to the two-year toxicity study in rats is required for evaluation in 2003:

- To assess whether some of the adverse effects that were observed were treatment-related, the groups treated with diacetyltartaric and fatty acid esters of glycerol should be compared with both untreated and monoglyceride-treated controls and the control groups should be compared with one another.
- Additional information on the incidence of mycocardial fibrosis and adrenal medullary hyperplasia in animals at the low and intermediate doses should be provided.

Monomagnesium phosphate, trisodium diphosphate

Information is required on the loss on drying, loss on ignition, test method for loss on ignition and assay method for the hydrates. This information is required for evaluation in 2003.

Natamycin

Information is required on the level and determination of water content, lead limit, specific rotation, assay value and method of assay for the commercial product. Comments on other aspects of the monograph are invited. This information is required for evaluation in 2003.

Quillaia extracts

The existing specifications for quillaia extracts were revised in order to clarify the differences between unpurified and semi-purified extracts Additional information on composition (minimum and maximum percentages of saponins unpurified and semi-purified extracts) is necessary, so the specifications were designated as tentative. Once the requested information has been received, the Committee will consider whether separate specifications for unpurified and semi-purified extracts are required. This information is required for evaluation in 2003. The ADI was made temporary pending clarification of the specifications. The temporary ADI is applicable only to the unpurified extract.

Annex 3

General considerations

An edited version of this section will appear in the report of the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It is reproduced here so that the information is disseminated quickly. This draft is subject to extensive editing.

1. Modification of the agenda

The following food additives were removed from the agenda (as announced in the *call for data*):

Annatto extracts	Scheduled for a future meeting, so that the Committee may consider toxicological studies that were being performed.
Amyloglucosidase from *Aspergillus oryzae,* var.	Included in the call for data by mistake
Sodium ethyl *para*-hydroxybenzoate	These food additives had been removed from the draft Codex General Standard for Food Additives and were referred to the Committee for evaluation. There was no indication that they are used as food additives and consequently little information was provided that would permit the establishment of ADIs or specifications.
Sodium propyl *para*-hydroxybenzoate	
Sodium methyl *para*-hydroxybenzoate	
calcium sulfite	
Sodium formate	
Calcium formate	
Synthetic ?-tocopherol	
Synthetic d-tocopherol	
Calcium tartrate	
Sorbitan trioleate	
Dipotassium diphosphate	
Dimagnesium diphosphate	
Phenyl salicylate (No. 906)	Had been evaluated previously at the fifty-fifth meeting (no. 736)*

*Corrected from the earlier version, where it was stated that no data were available.

2. Principles for the assessment of chemicals in food

The committee was informed that FAO and WHO are initiating a project to update and consolidate principles and methods for the assessment of chemicals in food, including food additives, contaminants, residues of veterinary drugs in food, and pesticide residues in food. This project is being undertaken on the basis of a recommendation of the *Conference on International Good Trade Beyond 2000: Science-based decisions, harmonization, equivalence, and mutual recognition* that was held in October 1999 and in view of the tremendous scientific advances and changes in the procedures and complexity of assessments of chemicals in food that have taken place since the publication of *Principles for the safety assessment of food additives and contaminants in food* (Environmental Health Criteria No. 70) and *Principles for the toxicological assessment of pesticide residues in food* (Environmental Health Criteria No. 104). It will be a comprehensive project that will include consideration of all those aspects of the assessment of chemicals in food that are considered by the Committee and the Joint FAO/WHO Meeting on Pesticide Residues.

The Committee recognized the importance of this initiative and recommended that it be undertaken as soon as possible.

3. Flavouring agents evaluated by the Procedure for the Safety Assessment of Flavouring Agents

The Committee questioned whether some of the substances included in the lists of flavouring agents that it had been requested to evaluate at its present meeting were in fact flavouring agents; some of these substances are used extensively in food processing as solvents, emulsifiers, or preservatives.

The Committee stressed that the Procedure for the Safety Evaluation of Flavouring Agents is intended for application to flavouring agents used to impart flavour to foods and not to non-flavour uses or to other chemicals that may be used in flavouring formulations. Consequently, the Committee was unable to finalize the evaluations of certain substances listed on the agenda[1], pending confirmation of their uses and intake as flavouring agents.

A clear definition of 'flavouring agent' has not been elaborated by the Committee. Although *Principles for the safety assessment of food additives and contaminants in food* provides some guidance, the Committee recommended that this issue be addressed at a future meeting.

4. Minimum assay values for flavouring agents

At its fifty-third meeting, the Committee established the criteria required for specifications for flavouring agents. The Committee noted that three criteria – chemical formula and relative molecular mass, identity test, and minimum assay value – constituted the core information required to establish acceptable specifications. At that time, the Committee expressed its view that a minimum assay value for individual flavouring agents of 95% applied to the content of the named flavouring agent or the named agent plus its known secondary components. About 90% of the flavouring agents evaluated to date meet or exceed the 95% minimum assay value for the named flavouring agent itself. For the others, the Committee received information on the nature of the secondary components. The Committee noted that 95% is not a fixed criterion for judging the acceptability of specifications for flavouring agents and that flexibility can be applied in establishing an acceptable level of secondary components, taking into account the likely levels of intake and other considerations.

Many secondary components are structurally related to the named flavouring agents and typically include small amounts of starting materials, isomers, and other flavouring agents. As these secondary components share many of the properties of the named flavouring agent, and in some cases are metabolites, they would not be expected to present a safety concern, or their safety can be determined from appropriate data on metabolism and toxicity.

The Committee noted that, in applying the Procedure for the Safety Evaluation of Flavouring Agents, information on secondary components included in the specification should be considered with data on intake and the potential toxicity of the flavouring agent and its structural analogues. The Committee therefore recommended that data on specifications be submitted before or at the same time as all other information necessary for evaluating safety.

5. Requests for data relating to intake assessments

The Committee recognized that it is not necessary to request data for intake assessments for all substances on its agenda, as it had done recently. Therefore, it developed criteria for determining when it is necessary to request such information. Calls for data should specify the information required for each substance on its agenda, as different data are required for the evaluation of food additives and contaminants.

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[1] The substances in question are benzoic acid (No. 850), glyceryl tribenzoate (No. 861), propylene glycol dibenzoate (No. 862), butyl-p-hydroxybenzoate (No. 870), glycerol (No. 909), 3-oxodecanoic acid glyceride (No. 914), 3-oxododecanoic acid glyceride (No. 915), 3-oxotetradecanoic acid glyceride (No. 916), 3-oxohexadecanoic acid glyceride (No. 917), glycerol monostearate (No. 918), glyceryl monooleate (No. 919), (tri)-Acetin (No. 920), glyceryl tripropionate (no. 921), (tri)-Butyrin (No. 922), glycerol 5-hydroxydecanoate (No. 923), glycerol 5-hydroxydodecanoate (No. 924), propylene glycol (No. 925), and propylene glycol stearate (No. 926).

Food additives

Data should be requested for the assessment of intake when food additives are evaluated for the first time or when they are re-evaluated, except for food additives:

- for which only specifications are to be considered and
- on which the committee has recently deferred an evaluation pending the provision of a specific toxicological study or specific information on specifications, provided the Committee has evaluated intake during the preceding 3-5 years.

For food additives included in the draft Codex General Standard for Food Additives (GSFA), information on proposed maximum levels should be provided in the call for data so that national intake assessments based on the maximum levels in the GSFA, national maximum levels, and/or actual levels of use can be submitted. The Committee has formulated data sheets for submission of national intake assessments, which are included in the guidelines for the preparation of working papers on the intake of food additives that are available from the Secretariat.

Contaminants

For contaminants, an intake assessment is required in all cases. The call for data should request data on:

- occurrence and concentration (both individual and summary data) from all available sources, preferably submitted in the GEMS/Food format, with information on sampling and analytical techniques, data quality and reliability, reporting conventions, and appropriate processing factors and
- national intake of the contaminant based on national surveys of food consumption and concentrations.

6. Inclusion of raw materials and manufacturing methods in specifications

With increasing volumes of food additives in international trade, it is becoming increasingly important that specifications include raw materials and methods of manufacture in order to provide a full account of the product that was evaluated. Without this information, a product could be produced from different materials by different methods; consequently, impurities might have arisen that were not considered during the toxicological evaluation of the substance.

Principles for the safety assessment of food additives and contaminants in food states that 'To establish the chemical identities of additives, it is necessary to know the nature of the raw materials, methods of manufacture and impurities. This information is used to assess the completeness of analytical data on the composition of additives, and to assess the similarity of materials used in biological testing with those commercially produced.'

Therefore, the specifications other than those for flavouring agents will include brief details of raw materials and methods of manufacture, excluding proprietary details. The level of detail should be similar to that already used in many specifications published by the committee for additives made by fermentation or from plant materials.

7. General specifications and considerations for enzyme preparations used in food processing

The Committee has, on many occasions, addressed issues related to specifications for enzyme preparations used in food processing. The General Specifications in use today for enzymes were first elaborated by the Committee at its twenty-sixth meeting. Several revisions have been made, including:

(1) an addendum to address issues related to enzymes from genetically modified microorganisms;
(2) addition of an appendix to describe the method for determining antibiotic activity;
(3) an amendment to address microbial strain numbers in the specifications for enzyme preparations; and
(4) addition of the general requirement that source microorganisms be non-pathogenic and non-toxigenic.

At its fifty-fifth meeting, the Committee requested that the General Specifications for enzymes be reviewed and revised. Special consideration was to be given to updating the specifications in light of recent technological advances and to ensure consistency and coherence.

The revised General Specifications require that all new enzyme preparations undergo a general safety assessment. Many of the requirements previously outlined for enzyme preparations from genetically modified microorganisms are appropriate for all preparations, regardless of source, and the present Committee revised the General Specifications to reflect those requirements. For enzymes from genetically modified sources, focus is now placed on the final microbial strain used as the source organism and the genetic material introduced into and remaining in the final microbial production strain.

At its fifty-fifth meeting, the Committee noted that the list of mycotoxins contained in the existing General Specifications was not relevant to all food enzyme preparations from fungal sources. It further agreed that an attempt to list all known mycotoxins of potential concern was impractical and unwarranted. At its present meeting, the Committee agreed that enzyme preparations derived from fungal sources be evaluated for those mycotoxins that are known to be produced by strains of the species used in the production of the enzyme preparation or related species.

With regard to limits on heavy metals, the Committee agreed that the specification for lead contained in the existing General Specifications should be lowered from 10 mg/kg to 5 mg/kg. The Committee recognized that arsenic is not a concern in enzyme preparations, and the limit for this metal was deleted. Moreover, as there is no traceable source of cadmium or mercury in enzyme preparations, the Committee saw no need to establish limits for those metals. Such changes are consistent with the Committee's current policy on heavy metals.

In considering microbiological contamination of enzyme preparations, the Committee agreed that the existing microbiological criteria (for *Salmonella* spp., *Escherichia coli*, and total coliforms) and the requirement that use of preparations not increase the total microbial count in treated food over the level considered to be acceptable for the respective food are sufficient to ensure microbial safety and were thus retained. The Committee noted that the specification for a total viable count of 5×10^4/g contained in the existing General Specifications is arbitrary and is not an indication of the safety of an enzyme preparation. Therefore, it was eliminated.

In considering allergenic potential, the Committee emphasized that when the source organism of an enzyme preparation is a genetically modified microorganism the need for an evaluation for allergenic potential of the gene products encoded by the inserted DNA should be assessed. The Committee agreed that when the DNA sequence of an enzyme from a genetically modified production microorganism is comparable to that coding for an enzyme already known to have a history of safe use in food, there would be no need to assess the allergic potential of that enzyme further.

Finally, the Committee recognized that the revised Specifications include many criteria for safety evaluation that would be more appropriately listed elsewhere. The Committee strongly recommended that *Principles for the safety assessment of food additives and contaminants in food* be revised to include the safety assessment of enzymes intended for use in food and subsequent removal of such guidelines from the General Specifications.

Annex 4

Contaminants

An edited version of this section will appear in the report of the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). It is reproduced here so that the information is disseminated quickly. This draft is subject to extensive editing.

1. 3-Chloro-1,2-propanediol

Certain chlorinated propanols occur as contaminants in hydrolysed vegetable proteins. Processing of defatted vegetable proteins by traditional hydrochloric acid hydrolysis leads to the formation of 3-chloro-1,2-propanediol and 1,3-dichloro-2-propanol. These two compounds were evaluated by the Committee at its forty-first meeting, when it concluded that 3-chloro-1,2-propanediol is an undesirable contaminant in food and considered that its concentration in hydrolysed proteins should be reduced to the lowest level technically achievable. Since that time, new data have become available, and the Codex Committee on Food Additives and Contaminants asked the Expert Committee to re-evaluate 3-chloro-1,2-propanediol.

Absorption, distribution, metabolism, and excretion

3-Chloro-1,2-propanediol crosses the blood-testis barrier and the blood-brain barrier and is widely distributed in body fluids. The parent compound is partly detoxified by conjugation with glutathione, resulting in excretion of the corresponding mercapturic acid, and is partly oxidized to ß-chlorolactic acid and further to oxalic acid. Approximately 30% is broken down to and exhaled as CO_2. In these studies, however, much of the administered dose was not accounted for. Intermediate formation of an epoxide has been postulated but not proven. There is some indication that microbial enzymes can dehalogenate haloalcohols to produce glycidol (a known genotoxin in vitro and in vivo).

Toxicological studies

The oral LD_{50} of 3-chloro-1,2-propanediol in rats is 150 mg/kg bw. In several studies in which the compound was given to rats at repeated doses in excess of 1 mg/kg bw per day, it decreased sperm motility and impaired male fertility. At doses of 10-20 mg/kg bw per day or more, alterations in sperm morphology and epididymal lesions (spermatocoele) were found in rats. 3-Chloro-1,2-propanediol reduced fertility in males of several other mammalian species at slightly higher doses than in the rat.

In rats and mice, 3-chloro-1,2-propanediol at doses of 25 mg/kg bw per day and above was associated with the development of dose-related central nervous system lesions, particularly in the brain stem.

In several short-term studies in rats and mice, the kidney was shown to be the target organ for toxicity. In a 4-week study in rats treated by gavage at 30 mg/kg bw per day, 3-chloro-1,2-propanediol increased the relative kidney weights. In a 13-week study in rats given an oral dose of 9 mg/kg bw per day a similar effect was seen.

In the pivotal long-term study in Fischer 344 rats, the absolute weight of the kidney was reported to be significantly increased by administration of 3-chloro-1,2-propanediol in drinking-water at all doses. Also at all doses tested, the incidence of tubule hyperplasia in the kidneys of animals of each sex was higher than in controls. Although the incidence did not reach statistical significance at the lowest dose tested (1.1 mg/kg bw per day), the Committee concluded that it represented part of a compound-related, dose-response relationship. Overt nephrotoxicity was seen at higher doses (5.2 and 28 mg/kg bw per day).

The results of most assays for mutagenicity in bacteria in vitro were reported to be positive, although negative results were obtained in the presence of an exogenous metabolic activation system from mammalian tissue. The results of assays in mammalian cells in vitro were also reported to be generally positive. It should be noted, however, that the concentrations used in all these assays were very high (0.1-9

mg/ml), raising serious questions about their relevance. The weight of the evidence indicates that 3-chloro-1,2-propanediol is not genotoxic in vitro at concentrations that do not cause toxicity. The results of assays conducted in vivo, including a test for micronucleus formation in mouse bone marrow and an assay for unscheduled DNA synthesis in rats, were negative. The Committee concluded that 3-chloro-1,2-propanediol was not genotoxic in vivo.

Altogether four long-term studies of toxicity and carcinogenicity were available; three (two with mice and one with rats) did not meet modern standards of quality. Nevertheless, none of the three studies indicated carcinogenic activity. In the fourth study, conducted in Fischer 344 rats, 3-chloro-1,2-propanediol was associated with increased incidences of benign tumours in some organs. These tumours occurred only at doses greater than those causing renal tubule hyperplasia, which was selected as the most sensitive end-point.

Occurrence

3-Chloro-1,2-propanediol has been detected at concentrations in excess of 1 mg/kg in only two food ingredients: acid-hydrolysed vegetable protein and soya sauce. In both ingredients, a range of concentrations has been reported, from below the limit of quantification (0.01 mg/kg with a method that has been validated in a range of foods and food ingredients) up to 100 mg/kg in some samples of acid-hydrolysed vegetable protein and more than 300 mg/kg in some samples of soya sauce.

Formation of 3-chloro-1,2-propanediol in acid-hydrolysed vegetable protein has been found to be related to production processes, and the concentration can be reduced markedly with suitable modifications. The source of 3-chloro-1,2-propanediol in soya sauce is being investigated; by analogy with hydrolysed vegetable protein, however, it may arise during acid hydrolysis in the manufacture of some products. Traditionally fermented soya sauces would not be contaminated with 3-chloro-1,2-propanediol.

3-Chloro-1,2-propanediol has also been quantified at low concentrations in a range of other foods and food ingredients, notably a number of cereal products that have been subjected to high temperatures, e.g., roasting or toasting. The concentrations are generally less than 0.1 mg/kg. Slightly higher concentrations (up to 0.5 mg/kg) have been found in food ingredients such as malt extracts, but the resulting concentrations in finished foods are below 0.01 mg/kg.

Estimates of dietary intake

Information on the concentrations of 3-chloro-1,2-propanediol in food, food ingredients, and protein hydrolysates was submitted by the United Kingdom, the USA, and the International Hydrolyzed Protein Council. The USA supplied a national estimate of the intake of 3-chloro-1,2-propanediol. Information on the consumption of soya sauce in Australia, Japan and the USA was also received.

At any level of intake that might reasonably be expected, 3-chloro-1,2-propanediol would not be expected to have acute effects. This analysis therefore addresses only long-term intake of 3-chloro-1,2-propanediol from its presence in foods.

The data submitted by the United Kingdom showed that 3-chloro-1,2-propanediol is found in some savoury foods, about 30% of samples containing concentrations above the limit of detection of 0.01 mg/kg. The mean residual concentration in these savoury foods was 0.012 mg/kg.

In a survey of 90 samples of commercially obtained soya sauces, 50 samples contained less than 1 mg/kg; the average concentration in the 90 samples was 18 mg/kg. The results of this survey were taken as representative of all soya sauces for the purpose of the intake assessment. Intake of 3-chloro-1,2-propanediol would be dominated by consumption of soya sauces contaminated with the compound.

When estimating the intake of 3-chloro-1,2-propanediol from food other than soya sauce, it was assumed that about one-eighth of the diet, 180 g (on the basis of 1500 g/day of solid food), consists of savoury foods that might contain 3-chloro-1,2-propanediol and that the mean residual concentration of

the compound in those foods is 0.012 mg/kg. On this basis, the intake of 3-chloro-1,2-propanediol from foods other than soya sauces is approximately 2 μg/person per day.

The mean and 90th percentile consumption of soya sauce that was used in the USA intake assessment were 8 and 16 g/person per day, respectively (consumers only), and the resulting estimate of intake of 3-chloro-1,2-propanediol was 140 μg/person per day for mean consumption and 290 μg/person per day for consumption at the 90th percentile. The mean consumption of soya sauce in Australia (consumers only) was approximately 11 g/person per day, and for consumers at the 95th percentile it was approximately 35 g/person per day, resulting in intake of 3-chloro-1,2-propanediol of 200 μg/person per day for mean consumption of soya sauce and 630 μg/person per day at the 90th percentile of consumption. Per-capita consumption of soya sauce in Japan (approximating a consumers-only consumption) was approximately 30 g/person per day, resulting in intake in Japan of 3-chloro-1,2-propanediol of approximately 540 μg/person per day for mean consumption of soya sauce. Intake at the 95th percentile in Japan would be 1100 μg/person per day by assuming consumption of soya sauce that is twice the mean.

Evaluation

The Committee chose tubule hyperplasia in the kidney as the most sensitive end-point for deriving a tolerable intake. This effect was seen in the long-term study of toxicity and carcinogenicity in rats in a dose-related manner, although the effect did not reach statistical significance at the lowest dose. The Committee concluded that the lowest-observed-effect level (LOEL) was 1.1 mg/kg bw per day and that this was close to a NOEL.

The Committee established a provisional maximum tolerable daily intake (PMTDI) of 2 μg/kg bw for 3-chloro-1,2-propanediol based on the LOEL of 1.1 mg/kg bw per day and a safety factor of 500, which included a factor of 5 for extrapolation from a LOEL to a NOEL. This factor was considered to be adequate to allow for the absence of a clear NOEL and to account for the effects on male fertility and for inadequacies in the studies of reproductive toxicity. Data available to the Committee indicated that the estimated mean intake of 3-chloro-1,2-propanediol by consumers of soya sauce would be at or above this PMTDI.

Impact of regulatory limits

As 3-chloro-1,2-propanediol is found infrequently in foods, a regulatory limit would be unlikely to have much effect on the overall intake of non-consumers of soya sauces. However, because the distribution of residual 3-chloro-1,2-propanediol in soya sauce is highly skewed and because it is likely that brand loyalty could result in regular consumption of highly contaminated brands of soya sauce, a regulatory limit on the concentration of 3-chloro-1,2-propanediol in soya sauce could markedly reduce the intake by soya sauce consumers.

2. 1,3-Dichloro-2-propanol

Since the time of the evaluation of the chloropropanols at the forty-first meeting, new data have become available, and the Codex Committee on Food Additives and Contaminants asked the Expert Committee to re-evaluate 1,3-dichloro-2-propanol.

Absorption, distribution, metabolism, and excretion

Approximately 5% of an oral dose of 1,3-dichloro-2-propanol was excreted in the urine of rats as ß-chlorolactate. About 1% of the dose was excreted as 2-propanol-1,3-dimercapturic acid. In another experiment, the urine of rats contained the parent compound (2.4% of the dose), 3-chloro-1,2-propanediol (0.35% of the dose), and 1,2-propanediol (0.43% of the dose). Epoxy-chloropropane (epichlorohydrin) was postulated to be an intermediate, which may either undergo conjugation with glutathione to form mercapturic acid or be hydrolysed to 3-chloro-1,2-propanediol. The latter undergoes oxidation to ß-chlorolactate, which is further oxidized to oxalic acid.

Toxicological studies

The oral LD_{50} of 1,3-dichloro-2-propanol in rats is 120-140 mg/kg bw. In several short-term rat studies, 1,3-dichloro-2-propanol at doses of 10 mg/kg bw per day and higher caused significant hepatic toxicity. This was associated with oxidative metabolism, which yielded intermediates that reacted with and depleted glutathione.

In a 13-week study in rats, overt hepatotoxicity, including increased liver weights, histological changes, and/or increased activity of serum alanine and aspartate transaminases, was seen after oral administration of 1,3-dichloro-2-propanol at 10 mg/kg bw per day and above. These doses also caused histopathological changes in the kidney, increased kidney weights, and alterations in urinary parameters. The NOEL was 1 mg/kg bw per day.

1,3-Dichloro-2-propanol has been reported to be hepatotoxic in humans exposed occupationally.

1,3-Dichloro-2-propanol was clearly mutagenic and genotoxic in various bacterial and mammalian test systems in vitro. The only available study in vivo showed no effect in a wing spot test in *Drosophila melanogaster.*

The results of the one long-term study of toxicity and carcinogenicity in rats confirmed the hepatotoxicity and the nephrotoxicity seen in the 13-week study. Furthermore, it demonstrated a clear carcinogenic effect of 1,3-dichloro-2-propanol at the highest dose tested, 19 mg/kg bw per day. The tumors (adenomas and carcinomas) occurred in liver, kidney, the oral epithelium and tongue, and the thyroid gland. No increase in tumour incidence was seen at the lowest dose tested, 2.1 mg/kg bw per day. Treatment-related non-neoplastic lesions of the liver were observed, sinusoidal peliosis being found in all treated groups.

Occurrence

Information on the concentrations of 1,3-dichloro-2-propanol in soya sauce was submitted by the USA. Additional information was derived from a published report on the concomitant occurrence of 3-chloro-1,2-propanediol and 1,3-dichloro-2-propanol in soya sauces. This information showed that 1,3-dichloro-2-propanol may be present in samples of hydrolysed vegetable protein and soya sauce that contain 3-chloro-1,2-propanediol at concentrations greater than 1 mg/kg. In those products in which 1,3-dichloro-2-propanol was quantifiable, the ratio of concentrations of 3-chloro-1,2-propanediol to 1,3-dichloro-2-propanol was at least 20.

Estimates of dietary intake

A report from the USA was used by the Committee to estimate the intake of 1,3-dichloro-2-propanol due to its presence in soya sauces. Information about the consumption of soya sauce was received from Australia, Japan, and the USA.

At any level of intake that might reasonably be expected, 1,3-dichloro-2-propanol would not be expected to have acute effects. This analysis therefore addresses only long-term intake of the compound from its presence in foods.

The intake of 1,3-dichloro-2-propanol from food other than soya sauce can be estimated roughly from data on residual concentrations of 3-chloro-1,2-propanediol in savory foods and the upper-bound 20:1 ratio of 3-chloro-1,2-propanediol:1,3-dichloro-2-propanol. If it is assumed that about one-eighth of the diet, 180 g (on the basis of 1500 g/day of solid food), consists of savory foods that might contain 1,3-dichloro-2-propanol and that the mean residual concentration of the compound in those foods is 0.0006 mg/kg, the background intake is approximately 0.1 µg/person per day.

The upper-bound 20:1 ratio of 3-chloro-1,2-propanediol concentration to that of 1,3-dichloro-2-propanol was used by the Committee to estimate the intake of 1,3-dichloro-2-propanol from consumption of soya sauce. The average concentration of 3-chloro-1,2-propanediol in a survey of 90 commercially

obtained soya sauce samples was 18 mg/kg; the residual concentration of 1,3-dichloro-2-propanol was therefore assumed to be 0.9 mg/kg.

The mean and 90th percentile consumption of soya sauce in the USA (consumers-only) is 8 and 16 g/person per day, respectively. The resulting estimate of the intake of 1,3-dichloro-2-propanol would be 7 μg/person per day at the mean level of consumption and 14 μg/person per day at the 90th percentile of consumption. The mean and 95th percentile consumption of soya sauces in Australia is approximately 11 and 35 g/person per day, respectively, resulting in estimates of intake of 10 and 30 μg/person per day for consumers at the mean and 90th percentiles, respectively. Per-capita intake of soya sauce in Japan (approximating a consumers-only intake) is 30 g/person per day, resulting in an estimate of intake for 1,3-dichloro-2-propanol of 27 μg/person per day. An upper percentile intake of 55 μg/person per day was estimated by assuming a consumption of soya sauce of two times the mean.

Evaluation

Although only a few studies of kinetics, metabolism, short- and long-term toxicity, and reproductive toxicity were available for evaluation, they clearly indicated that 1,3-dichloro-2-propanol was genotoxic in vitro, was hepatotoxic, and induced a variety of tumours in various organs in rats. The Committee concluded that the estimation of a tolerable intake was inappropriate because of the nature of the toxicity based on the following considerations:

- The results of the long-term toxicity/carcinogenicity study showed significant increases in the incidences of both benign and malignant neoplasms in at least three independent tissues.
- It has been shown unequivocally that this contaminant can interact with chromosomes and/or DNA; however, the tests were confined to bacterial and mammalian test systems in vitro, and there were no data on intact mammalian organisms or humans.

The Committee noted that the dose that caused tumours in rats (19 mg/kg bw per day) was about 20 000 times the highest estimated intake of 1,3-dichloro-2-propanol by consumers of soya sauce (1 μg/kg bw per day).

The available evidence suggests that 1,3-dichloro-2-propanol is associated with high concentrations of 3-chloro-1,2-propandiol in food. Regulatory control of the latter would therefore obviate the need for specific controls on 1,3-dichloro-2-propanol.

3. Polychlorinated dibenzodioxins, polychlorinated dibenzofurans, and coplanar polychlorinated biphenyls

Introduction

Polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are by-products of combustion and of various industrial processes, and they are widely present in the environment. Polychlorinated biphenyls (PCBs) were manufactured in the past for a variety of industrial uses, notably as electrical insulators or dielectric fluids and specialized hydraulic fluids. Most countries banned manufacture and use of PCBs in the 1970s; however, past improper handling of PCBs constitutes a continuing source of PCBs in the environment, and disposal of equipment now in use poses some risk of further contamination.

Neither PCDDs nor PCDFs have been evaluated previously by the Committee. PCBs were evaluated at the thirty-fifth meeting, when a provisional tolerable weekly intake (PTWI) could not be established because of the limitations of the available data and the ill-defined nature of the materials that were used in feeding studies.

PCDDs, PCDFs, and coplanar PCBs were evaluated at the present meeting on the basis of a request by the Codex Committee on Food Additives and Contaminants to evaluate the risks associated with their presence in food.

The Committee evaluated the PCDDs, PCDFs, and coplanar PCBs for which toxic equivalency factors (TEFs) for mammals have been derived by WHO. Table 1 summarizes the compounds that were considered and their assigned TEF values. The TEF approach relates the toxicity of all chemicals in the series to 2,3,7,8-TCDD, one of the most potent of the chemicals on which most toxicological and epidemiological information was available. Use of the TEF concept rests on the assumption that PCDDs, PCDFs, and coplanar PCBs have a common mechanism of action, which involves binding to the aryl hydrocarbon (Ah) receptor, an intracellular receptor protein. This binding is considered to be the necessary first, but not sufficient, step in expressing the toxicity of these compounds. Many uncertainties exist in use of the TEF approach for human risk assessment, but pragmatically it is the most feasible approach that is available.

Table 1. Compounds considered and their assigned TEFs

Compound	WHO TEF value	Compound	WHO TEF value
Dibenzodioxins		*"Non-ortho" PCBs*	
2,3,7,8-TCDD	1	3,3'4,4'-TCB (PCB #77)	0.0001
1,2,3,7,8-PeCDD	1	3,4,4'5-TCB (#81)	0.0001
1,2,3,4,7,8-HxCDD	0.1	3,3,'4,4,'5-PeCB (#126)	0.1
1,2,3,6,7,8-HxCDD	0.1	3,3',4,4'5,5'-HxCB (#169)	0.01
1,2,3,6,7,9-HxCDD	0.1		
1,2,3,4,6,7,8-HpCDD	0.01	*"Mono-ortho" PCBs*	
OCDD	0.0001	2,3,3',4,4'-PeCB (#105)	0.0001
Dibenzofurans		2,3,4,4',5-PeCB (#114)	0.0005
2,3,7,8-TCDF	0.1	2,3',4,4',5-PeCB (#118)	0.0001
1,2,3,7,8-PeCDF	0.05	2,3',4,4',5'-PeCB (#123)	0.0001
2,3,4,7,8-PeCDF	0.5	2,3,3',4,4',5-HxCB (#156)	0.0005
1,2,3,4,7,8-HxCDF	0.1	2,3,3',4,4',5'-HxCB (#157)	0.0005
1,2,3,6,7,8-HxCDF	0.1	2,3',4,4',5,5'-HxCB (#167)	0.00001
1,2,3,7,8,9-HxCDF	0.1	2,3,3',4,4',5,5'-HbCB (#189)	0.00001
2,3,4,6,7,8-HxCDF	0.1		
1,2,3,4,6,7,8-HpCDF	0.01		
1,2,3,4,7,8,9-HpCDF	0.01		
OCDF	0.0001		

A WHO consultation held in 1998 established a tolerable daily intake (TDI) of 1-4 pg/kg bw, which was applied to the toxic equivalents (TEQs) of PCDDs, PCDFs, and coplanar PCBs. The TDI was based on a number of studies of developmental toxicity, in which pregnant rats were given 2,3,7,8-TCDD by gavage, and immunological toxicity. The present Committee used this assessment as the starting point for its evaluation, taking into account newer studies that provided information on:

- toxicokinetics in a comparison of the fetal transfer of TCDD after bolus and repeated dosing;
- two new studies of developmental toxicity; and
- new information on the study in rhesus monkeys that placed its results in question.

Toxicokinetics

Coplanar compounds in dietary fat pass easily from the gastrointestinal tract into the blood. Indeed, experiments in humans and animals show 50-90% absorption of orally administered 2,3,7,8-TCDD. This figure is comparable with the near-complete absorption of PCDDs, PCDFs, and PCBs by nursing infants from their mothers' milk.

After absorption from the gastrointestinal tract, 2,3,7,8-TCDD enters the lymph in the form of chylomicrons and is then cleared from the blood within 1 h. Cleared 2,3,7,8-TCDD appears mainly (74-81% of an administered dose) in the liver and adipose tissue. After clearance of chylomicrons, coplanar

compounds remain mainly in serum lipoproteins (very low density, low density, and high density) and some are bound to serum proteins.

The Committee used the results of a study in which the radiolabel was measured in the tissues of pregnant Long-Evans rats one day after administration of 50, 200, 800, or 1000 ng/kg bw [^{3}H]2,3,7,8-TCDD by gavage on day 15 of gestation. The average maternal body burdens (with the percentage of the dose) were 31 (60%), 97 (48%), 520 (65%), and 580 (59%) ng/kg bw, respectively. On the basis of this study, the Committee used a value of 60% for the amount of 2,3,7,8-TCDD retained in pregnant rats one day after administration of a single dose by gavage on day 15 of gestation.

The distribution of PCDDs and PCDFs between the serum and organs is governed by lipid partitioning and protein binding. The concentrations of PCDDs and PCDFs in blood and adipose tissue correlate well. TCDD is distributed between plasma or blood and adipose tissue by lipid partitioning, whereas the distribution of HxCDD/HxCDF and OCDD/OCDF are governed by both lipid partitioning and plasma protein binding.

In the liver, protein binding plays an important role in the uptake of coplanar compounds from the blood, even for lower chlorinated congeners. When rodents are exposed to increasing doses of 2,3,7,8-TCDD, it is preferentially sequestered in the liver, so that the concentration in the liver exceeds that in adipose tissue by many times. The biochemistry of this phenomenon is as follows: After entering liver cells, 2,3,7,8-TCDD either dissolves in the lipid fraction or binds to the Ah receptor or cytochrome P450 (CYP) proteins, probably microsomal P4501A2. As the amount of CYP1A and 1B proteins in cells is regulated by formation of the TCDD-Ah receptor complex, exposure to increasing amounts of TCDD triggers a cascade of events involving increased TCDD entering the cell, increased formation of the TCDD-Ah receptor complex, increased formation of CYP1A and 1B mRNA and protein (enzyme induction), and accumulation of TCDD by increased binding to the induced CYPs. Similar sequestration has been observed with higher chlorinated PCDDs and PCDFs and with coplanar PCBs.

The hepatic sequestration of coplanar compounds markedly affects the distribution of these compounds in the body. For example, whereas the liver contributes 10% and the adipose tissue 60% to the body burden of TCDD in uninduced mice containing only constitutive concentrations of hepatic CYP, these fractions may increase to 67% in liver and decrease to 23% in fully induced mice containing both constitutive and induced hepatic CYP protein concentrations. Similar results were found in rats, clearly indicating the non-linear character of the kinetics of TCDD at concentrations that induce hepatic CYP proteins.

As in rodents, preferential sequestration of PCDDs and PCDFs in the liver rather than in adipose tissue has been observed in humans exposed to background concentrations of these compounds. This sequestration is probably due to binding to constitutive CYP proteins for, although Ah receptor-dependent CYP induction has been observed in human liver cells in vitro after exposure to TCDD (induction at 1 pmol/L; EC_{50} ~ 100 pmol/L), it occurred at concentrations that were several orders of magnitude higher than those observed in human blood.

Metabolism and excretion

In experimental animals, PCDDs and PCDFs are excreted almost exclusively in the bile, excretion in the urine being a minor route. Whereas the parent compound is found primarily in the organs of rodents, only metabolites of PCDD and PCDF occur in bile, indicating hepatic metabolism, including hydroxylation and conjugation, of these compounds. Similar reactions have been found in vitro in incubated recombinant human liver enzyme (metabolism of 2,3,7,8-TCDF by CYP1A1). Faecal excretion of unmetabolized PCDDs and PCDFs is also an important route of elimination in humans.

In rodents, the terminal half-time of 2,3,7,8-TCDD ranges from 8-24 days in mice to 16-28 days in rats. Humans eliminate PCDDs and PCDFs more slowly, the estimated mean half-time of TCDD ranging from 5.5 to 11 years. The half-lives of other PCDD congeners and of PCDFs and coplanar PCBs

vary widely. The TEFs (Table 1) take into account, to some extent, the differences in half-time between different congeners.

Relationship between human intake and doses used in animal studies

The biochemical and toxicological effects of PCDDs, PCDFs, and coplanar PCBs are directly related to tissue concentrations and not to the daily dose. The most appropriate dose measure would therefore be the concentration at the target tissue; however, this is seldom known. The body burden, which is strongly correlated with tissue and serum concentrations, integrates the differences in half-lives between species. Thus, rodents require appreciably higher daily doses (100-200-fold) to reach a body burden at steady state equivalent to that recorded in humans exposed to background concentrations. Toxicokinetically, estimates of body burden are therefore more appropriate measures of dose for interspecies comparisons than daily dose.

The long half-lives of PCDDs, PCDFs, and coplanar PCBs has several implications for the period of intake of relevance to the assessment. First, the TEQs in the body (or the internal TEQs to which a target organ is exposed) will rise over time as more of the compounds are ingested. Second, after cessation of exposure, the body's stored TEQs (and the exposure of internal organs) will decline slowly, only half of the accumulated TEQs disappearing over about 7 years, resulting in a pseudo steady state only after decades. Third, because of this long-term storage in the body and the consequent daily exposure to the body's stored TEQs, a person's ingestion on a particular day will have a small or even negligible effect on the overall body burden. For example, food contamination that leads to an intake 100 times the amount in a typical meal – an event not expected to occur – would result in less than a 3% increase in the body burden of an adult eating that meal. The rest of the person's body burden would be made up of the PCDDs, PCDFs, and coplanar PCBs consumed in the many thousands of past meals over the previous decade or more.

Therefore, the Committee concluded that the appropriate averaging period for evaluating intake of these compounds is one month or more.

In order to transform an animal body burden into an equivalent human monthly intake (EHMI) that on a long-term basis would lead to a similar body burden (at steady state), simple, classical toxicokinetic calculations can be used. The elimination of PCDDs at low doses was considered to follow first-order kinetics and to be independent of the body burden or dose. Equation 1 describes the relationship between the total steady-state body burden and intake assumed by the Committee.

Equation 1
Body burden at steady state (ng/kg bw) = f * intake (ng/kg bw per day) * half-time in days/ln(2)

where f is the fraction of dose absorbed (assumed to be 50% for absorption from food for humans) and the estimated half-time of 2,3,7,8-TCDD is 2774 days (7.6 years). For compounds that follow first-order kinetics, four to five half-lives will be required to approach steady state. For TCDD, this would be equivalent to more than 30 years.

This model is based on the assumption that PCDDs are distributed in only one compartment (the whole body). Although most of the body burden of PCDD is distributed in the lipid stores, at higher doses the liver also sequesters these compounds to some extent in both humans and animals. Predictions of body burden that are based on lipid concentrations after intake of high concentrations may therefore underestimate the total body burden (and the intake leading to that body burden) because of hepatic sequestration. Use of physiologically based pharmacokinetic models may be more appropriate under these circumstances. For the low concentrations to which the general human population is exposed and for the low doses used in the relevant pivotal toxicological studies, the Committee considered use of a less complicated, classical pharmacokinetic model appropriate for transformation of body burdens into estimated human daily intakes.

Exposure of the fetus in developmental toxicity studies

The time of dosing in several of the studies considered by the Committee, day 15 of gestation, marks the onset of the sensitive phase of sexual differentiation in rats and represents a critical time of fetal exposure. The determinant of the reproductive effects is the fetal concentration on day 15-16 of gestation. As placental transfer is mediated *via* the blood, the extent of fetal exposure is determined by the serum concentration, which may differ with a bolus dose (as in these studies) and with repeated doses providing the same total intake. As the serum concentration of 2,3,7,8-TCDD after a bolus dose rises before redistribution to the tissue compartments, the serum concentration is likely to be higher than after long-term intake of a lower concentration.

The difference in the fetal body burden after a single bolus dose and after repeated administration of a low dose resulting in a similar maternal body burden was addressed in a study in which radiolabel was measured in both maternal and fetal tissues of Long Evans dams at day 16 of gestation (Hurst et al, 2000a,b). The rats were dosed by gavage with [^{3}H]2,3,7,8-TCDD at 1, 10, or 30 ng/kg bw per day in corn oil, 5 days per week, for 13 weeks. They were then mated, and dosing was continued daily throughout gestation. The regimen produced a steady-state concentration of 2,3,7,8-TCDD in the dams. The average maternal and fetal body burdens at day 16 of gestation after this treatment and after a single administration of 2,3,7,8-TCDD by gavage on day 15 of gestation are shown in Table 2.

Table 2. Average maternal and fetal body burdens after a single dose and after administration of repeated doses of 2,3,7,8-TCDD to pregnant rats

Single dose on day 15 of gestation			Administration of repeated doses		
Single dose (ng/kg bw)	Body burden measured at day 16 of gestation		Adjusted daily dose (ng/kg bw per day) [a]	Body burden measured at day 16 of gestation	
	Maternal (ng/kg bw)	Fetal (ng/kg bw)		Maternal (ng/kg bw)	Fetal (ng/kg bw)
50	30	5.3	0.71	20	1.4
200	97	13	7.1	120	7.5
800	520	39	21	300	15
1000	590	56			

From Hurst *et al.*, 2000a,b

[a]Adjusted for continuous administration from 5 to 7 days per week

As expected, a single dose on day 15 of gestation by gavage resulted in considerably higher fetal concentrations on day 16 than short-term administration of low daily doses leading to maternal steady-state body burdens of similar magnitude.

Using the data in Table 2, the Committee conducted least-squares linear fits of dose versus maternal and fetal body burdens. Since radiolabelled 2,3,7,8-TCDD was used in both studies, a zero intercept was assumed for the fitted line. None of these fits showed what appeared to be any significant deviation from linearity. These data indicate that the ratio of fetal to maternal body burden would be 1.7 times higher from a bolus dose than from repeated dosing that providing the same total dose. Kinetic data indicate that a linear dose relationship would be expected at the dose ranges used in these studies. The fetal versus maternal body burdens in both data sets could also be fit to power equations, which provided a better fit of the data in the lower dose range of the single-dose experiments. The factor used to convert maternal body burden following acute dosing into a corresponding steady-state body burden using the power equations was 2.6.

Toxicological and epidemiological studies

Acute toxicity

In experimental animals, the acute toxicity of TCDD and related PCDDs and PCDFs substituted in at least the 2, 3, 7, and 8 positions varies widely between and among species. For example, the oral LD_{50} in

guinea-pigs was 0.6 µg/kg bw, while that in hamsters was greater than 5000 µg/kg bw. Explanations for this variation include Ah receptor functionality (size, transformation, and PCDD response element binding), toxicokinetics (metabolic capacity and tissue distribution), and body fat content. While data on acute toxicity were available for various commercial PCB mixtures (LD_{50} values usually greater than 100 mg/kg bw), the data on the individual coplanar PCB congeners in mammals were limited. Ah-responsive rodent species tend to have lower LD_{50} values.

One of the commoner symptoms associated with PCDD-induced acute lethality is a generalized delayed wasting syndrome characterized by inhibition of gluconeogenesis, reduced feed intake, and loss of body weight. Although some species differences exist, other toxic effects observed after acute exposure to PCDDs include haemorrhages in a number of organs, thymic atrophy, reduced bone-marrow cellularity, and loss of body fat and lean muscle mass.

Developmental toxicity

A number of biochemical changes, such as enzyme induction, altered expression of growth factors and enhanced oxidative stress, have been noted in experimental animals with 2,3,7,8-TCDD body burdens within a lower range of 3-10 ng/kg bw. The Committee considered these biochemical effects to be early markers of exposure to PCDDs, PCDFs, and coplanar PCBs or events induced by these compounds in animals and in humans that may or may not result in adverse effects at higher body burdens.

The Committee reviewed the relevant studies included in the 1998 WHO evaluation published in *Food Additives and Contaminants*, 2000 (Gehrs et al., 1997; Gehrs & Smailowicz, 1999; Gray et al., 1997a,b; Mably et al., 1992a,b,c; Rier et al., 1993;) and identified two additional recent studies (Faqi et al., 1998; Ohsako et al., 2001). The Committee noted that the most sensitive adverse effects reported were on development in the male offspring of rats and immunological deficits after prenatal exposure to 2,3,7,8-TCDD (see Table 3).

Table 3. Summaries of the studies presenting the lowest NOELs and LOELs for the most sensitive adverse effects of 2,3,7,8-TCDD on developmental end-points in experimental animals.[a]

Study/ Rat strain	End-point	Dosing regimen	NOEL body burden (ng/kg bw)	LOEL body burden (ng/kg bw)
Ohsako et al. (2001) Holtzman	Ventral prostate weight; decreased anogenital distance in male offspring	Single oral gavage bolus gestation day 15	13	51
Faqi et al. (1998) Wistar	Decreased sperm production and altered sexual behavior in male offspring	Loading dose/maintenance dose by subcutaneous injections		25
Gray et al. (1997) Long Evans	Accelerated eye opening and decreased sperm count in offspring	Single oral gavage bolus gestation day 15		28
Mably et al. (1992c) Holtzman	Decreased sperm count in offspring	Single oral gavage bolus gestation day 15		28
Gehrs et al (1997); Gehrs and Smailowicz (1998) F344	Immune suppression in offspring	Single oral gavage bolus gestation day 14		50

[a] Body burdens estimated using a linear fit to the data in Table 2.

The 1998 WHO consultation identified a study that found endometriosis after long-term administration of TCDD to rhesus monkeys. The Committee stressed that the reported findings in this study

should be interpreted with caution, as the daily intake was not adequately reported. In addition, analyses conducted 13 years after termination of exposure identified increased concentrations of coplanar PCBs in the blood of the monkeys with endometriosis, possibly due to an unknown source of PCB. The Committee also noted that some of the pivotal studies in rats (Table 3) would result in similar or lower equivalent EHMIs than that obtained from the LOEL for endometriosis in monkeys.

In a recent study (Ohsako et al., 2001), pregnant Holtzman rats were given a single oral dose of 2,3,7,8-TCDD at 0-800 ng/kg bw on day 15 of gestation, and the male offspring were examined on days 49 and 120 after birth. No changes were seen in testicular or epididymal weight nor in daily sperm production or sperm reserve at any dose. However, the weight of the urogenital complex, including the ventral prostate, was significantly reduced at doses of 200 and 800 ng/kg bw in rats killed on day 120. Moreover, the anogenital distance of male rats receiving doses of 50 ng/kg bw or above and killed at this time was significantly decreased. The Committee noted that administration of 2,3,7,8-TCDD at any dose resulted in a dose-dependent increase in 5a-reductase type 2 mRNA and a decrease in androgen receptor mRNA in the ventral prostate of rats killed at day 49 but not in those killed at day 120, with no adverse sequelae at the lowest dose of 12.5 ng/kg bw. On the basis of 60% absorption and an assumption of a linear relationship estimated for the data in Table 2, the equivalent maternal body burden after multiple doses at this NOEL would be 13 ng/kg bw. Using the power model to fit the data in Table 2, the body burden LOAEL was estimated to be 19 ng/kg bw. The LOEL of 50 ng/kg bw per day corresponds to an equivalent body burden of 51 ng/kg bw using the linear and 76 ng/kg bw using the power model.

The lowest LOAEL reported for the reproductive system of the male offspring used Wistar rats (Faqi et al 1998). In this study, the dams were treated subcutaneously prior to mating and throughout mating, pregnancy and lactation. They received an initial loading dose of 25, 60, or 300 ng ^{14}C-2,3,7,8-TCDD/kg bw 2 weeks prior to mating, followed by weekly maintenance doses of 5, 12, or 60 ng 2,3,7,8-TCDD/kg bw. The size of the maintenance doses was based on a reported elimination half-time of 3 weeks for adult rats. Effects on male reproduction were studied on postnatal days 70 and 170. The number of sperm per cauda epididymis was reduced in all treated groups at puberty and at adulthood. Daily sperm production was permanently decreased, as was the sperm transit rate in the male offspring that were administered 2,3,7,8-TCDD, thus increasing the time required by the sperm to pass through the cauda epididymis. Moreover, the male offspring of the treated groups showed an increased number of abnormal sperm when investigated at adulthood. Mounting and intromission latencies were significantly increased in the low- and high-dose groups, but not in the mid-dose group. The Committee noted the lack of a clear dose-response relationship for most of these effects in the treated groups. In the high-dose group, the concentration of serum testosterone was decreased at adulthood and permanent changes in the testicular tubuli included pyknotic nuclei and the occurrence of cell debris in the lumen. The fertility of the male offspring was not affected in any of the treated groups.

To compute the long-term dose required to produce the fetal concentration in the dose group given the initial loading dose of 25 ng/kg bw, it should be noted that this dosing pattern would have been reduced to 20 ng/kg bw prior to the maintenance dose of 5 ng/kg bw given on day 14. Based on the linear fit to the data in Table 2, the fetal body burden resulting from the maternal body burden of 20 ng/kg bw would be 1.04 ng /kg bw. The maintenance dose of 5 ng/kg bw administered on gestation day 14 would produce an additional contribution to the fetal body burden of 0.27 ng/kg bw resulting in a total fetal body burden of 1.31 ng/kg bw. Based on a linear fit to the data in Table 2, a maternal body burden of 25 ng 2,3,7,8-TCDD/kg bw at steady state would be needed to produce this fetal body burden.

The studies described in Table 3 provide evidence of adverse effects on the reproductive system in the male offspring of pregnant rats administered 2,3,7,8-TCDD. The studies demonstrate reduction in daily sperm production, cauda epididymal sperm number and epididymis weight as well as accelerated eye opening, reduction in anogenital distance and feminised sexual behaviour in the male offspring associated with maternal steady-state body burdens in the range of 25 ng 2,3,7,8-TCDD/kg bw and above. Reductions in the weights of testes and the size of sex-accessory glands, such as the ventral prostate in the male offspring, and development of external malformations of genitalia in female offspring as well as reduced male and/or female fertility require higher maternal body burdens. The Committee noted that the

most sensitive end-points identified differed between studies. This might reflect strain differences in sensitivity and/or even minor differences in the experimental conditions, e.g. the diet. The Committee also noted that in one study a single maternal gavage dose of 12.5 ng 2,3,7,8-TCDD/kg bw produced a decrease in the androgen receptor mRNA level in the ventral prostate at puberty on post-natal day 49, indicative of reduced androgenic responsiveness. However, at this dose level none of the above-mentioned adverse effects were seen in the male offspring. This dose corresponds to an estimated maternal steady-state body burden of approximately 19 ng 2,3,7,8-TCDD/kg bw (Table 3). As with enzyme induction, altered expression of growth factors and enhanced oxidative stress, the Committee considered this effect to be an early marker of exposure to 2,3,7,8-TCDD or an event induced in animals that may or may not result in adverse effects at higher body burdens.

Genotoxicity

Several short–term assays for genotoxicity with 2,3,7,8-TCDD covering various end-points were primarily negative. Furthermore, TCDD does not bind covalently to DNA from the liver of mice. The Committee concluded that TCDD is not an initatiator of carcinogenesis.

Carcinogenicity studies in animals

2,3,7,8-TCDD and other PCDDs induced tumours at multiple sites in studies with multiple animal species in both sexes. In a series of in vivo and in vitro assays TCDD displayed the capacity to promote growth of transformed cells (e.g. rat tracheal epithelium cells treated with *N*-methyl-*N*'-nitro-*N*-nitrosoguianidine), consistent with observations of cancer promotion in whole animals. In a long-term study of carcinogenicity of TCDD in rats, the LOEL for hepatic adenomas in females was 10 ng/kg bw per day. The NOEL was 1 ng/kg bw per day. Several studies have shown that 2,3,7,8-TCDD promotes tumours in experimental animals, in particular liver tumours. Several other PCDDs, PCDFs, and non-ortho- and mono-ortho-PCBs also promoted liver tumours. In a long-term study in rats in which the incidence of liver tumours was increased, the LOEL (10 ng/kg bw per day) corresponded to a steady-state body burden of 290 ng/kg bw. In order for humans to attain a similar steady-state body burden, they would have to have a daily intake of 150 pg/kg bw (Equation 1).

Non-cancer effects in humans

In two episodes of food poisoning in Japan and Taiwan in which infants were exposed *in utero* to heat-degraded PCBs a variety of adverse physical developmental abnormalities were observed, such as decreased penis length and alterations of spermatozoa; neurodevelopmental abnormalities were also seen. The affected children in Taiwan were born to mothers with estimated TEQ body burdens of 2-3 µg/kg bw.

For cohorts of infants in Germany, the Netherlands, and the USA, effects of exposures that could be considered environmental or background were evaluated at the time the studies were conducted; for example, the mean concentration of TEQs in human milk was 60 pg/g of lipid (range 25–155) in a study in Rotterdam and Groningen. Low birth weight and detriments in neurological development were observed in several of these studies, and alterations in thyroid hormones, lymphocyte subpopulations, infections, and respiratory symptoms were observed in specific studies. The observed neurodevelopmental deficits were subtle, were within the normal range, and their potential consequences for future intellectual function are unknown. The associations observed were considered to be due to prenatal (*in utero*) exposure rather than to postnatal intake (human milk). In one study of breast-fed and bottle-fed infants, the intake of PCDDs and PCBs was inversely related to performance in neurobehavioural tests; breast-fed infants performed better in neurobehavioural tests than bottle-fed infants. The studies of low exposure primarily addressed PCBs, while fewer data were available on the effects of PCDDs and PCDFs.

In adults, most of the non-cancer effects observed after exposure to PCDDs, PCDFs, and coplanar PCBs, such as chloracne, appeared only at doses several orders of magnitude greater than those generally due to background contamination of foods. In Seveso, more female children than expected were born to fathers with serum TCDD concentrations > 80 pg/g of lipid (16-20 ng/kg bw) at the time of conception.

Carcinogenicity in humans

A working group convened by the International Agency for Research on Cancer (IARC) classified 2,3,7,8-TCDD as a human carcinogen (Group 1) on the basis of limited evidence in humans and sufficient evidence in experimental animals as well as on mechanistic considerations. The other PCDDs and PCDFs were considered not to be classifiable as to their carcinogenicity to humans (Group 3).

The most informative studies for an evaluation of the carcinogenicity of 2,3,7,8-TCDD are four cohort studies of herbicide producers (two in Germany and one each in the Netherlands and the USA) and one cohort study of residents of a contaminated area in Seveso, Italy. A multi-country cohort study from IARC included three of these four cohorts and other industrial cohorts, many of which had not been reported in separate publications, as well as some professional herbicide applicators.

In most of the epidemiological studies considered, exposure had been primarily to TCDD, with some exposure to mixtures of other PCDDs, as contaminants of phenoxy herbicides and chlorophenols. The studies involved persons with the highest recorded exposure to 2,3,7,8-TCDD, with estimated geometric mean blood lipid concentrations after the last exposure ranging from 1100 to 2300 pg/g of lipid in the industrial cohorts and lower average concentrations among persons exposed in Seveso.

Low excess risks on the order of 40% were found for all neoplasms combined in all the studies of industrial cohorts in which the exposure assessment was adequate. Risks for cancers at specific sites were increased in some of the studies, but the results are not consistent between studies and no single cancer site seemed to predominate. Tests for trends to increasing excess risks for all neoplasms combined with increasing intensity of exposure were statistically significant. Increased risks for all neoplasms with time since first exposure were observed in those studies in which latency was evaluated. The follow-up of the Seveso cohort has been shorter than for the industrial cohorts; however, the rate of death from all cancers has not differed significantly from that expected in the general population. Excess risks were seen for cancers at some specific sites in the most heavily contaminated zones, but the numbers of cases are small.

In these well-conducted cohort studies, therefore, increasing intensity of exposure could be ascertained with precision because of the long biological half-time of TCDD in human tissues, and the relative risks increased significantly with increasing exposure. Although the excess cancer risk at the highest exposure was statistically significant, these results must be evaluated with caution, as the overall risks are not high and the strongest evidence is for industrial populations with two to three orders of magnitude greater exposure than the general population who also had heavy exposure to other chemicals; furthermore, lifestyle factors such as smoking were not evaluated. There are few precedents of carcinogens that cause an increase the risk of cancer for all tumours combined, without an excess risk for any tumour predominating.

The calculation of a "benchmark dose" was explored (e.g., the ED_{01} (effective dose), the dose estimated to result in a 1% increase in cancer mortality), on the basis of a meta-analysis of data on three industrial cohorts with well-documented exposure, for comparison with non-cancer effects. A statistically significant linear trend in risk with exposure was observed, which persisted even after exclusion of groups with the highest exposure. Within the range of reasonable assumptions, the ED_{01} ranged quite widely and strongly depended on the assumptions made. Furthermore, a number of uncertainties exist that would influence the predicted ED_{01}, including the exposure of the occupational cohorts and, to a lesser extent, potential confounding effects of factors not considered in the studies.

Sampling and analytical methods

No specific guidelines have been drawn up for sampling foods to be analysed for their PCDD, PCDF, and coplanar PCB content. The basic guidelines for sampling of organic contaminants or pesticides should therefore be used. The objective is to obtain a representative, homogeneous laboratory sample without introducing secondary contamination. Although PCDDs, PCDFs, and coplanar PCBs are chemically stable, the storage and transport of samples should ensure that they do not deteriorate. PCDDs, PCDFs, and coplanar PCBs are usually found as complex mixtures of varying composition in different matrices.

Their identification and quantification requires a highly sophisticated analysis, because the toxic congeners as presented in Table 1 must be separated from the more prevalent and less toxic congeners. Usually, PCDDs, PCDFs, and coplanar PCBs are determined by capillary gas chromatography with mass spectrometry (GC/MS).

No official method exists for the determination of these compounds in food. Reliable results can be obtained in the absence of official methods if the method used has been shown to fit the purpose and to fulfil analytical quality criteria developed in other fields of residue analyses. The methods used to determine PCDDs and PCDFs in food must be capable of providing sufficient information to calculate results as TEQs at 0.1-1 pg/g of fat in milk, meat, and eggs, around 10 pg/g of fat in fish or up to 100 pg/g of fat or more in cases of higher contamination, and 0.1-0.5 pg/g of dry matter for TEQs in food of vegetable origin. The patterns of congeners can vary between regions and foods.

Particularly when the method used is of insufficient sensitivity, the concentrations of PCDDs, PCDFs, and coplanar PCBs in many foods may be near or below the limit of quantification. The method used to derive the concentrations of undetected congeners (the imputation method) can therefore have a variable effect on the summary TEQ value for a food sample. The most commonly used imputation methods calculate the contribution of each non-detected congener to the TEQ either as zero ("lower bound concentrations"), as the limit of detection/limit of quantification ("upper bound concentrations") or as half the limit of detection/determination. For methods with insufficient sensitivity, the factor for differences between lower- and upper-bound concentrations can be in the range of 10 to 100, in extreme cases even higher. If sensitivity is appropriate, there are negligible differences between lower- and upper-bound concentrations in the relevant ranges. Therefore, low estimates of PCDDs, PCDFs, and coplanar PCBs may represent truly low concentrations in the sample or be the result of use of zero as the factor for undetected congeners in a food sample. Conversely, high estimates may be the result of a real contamination or of application of the upper-bound concept with insufficient sensitivity.

Application of upper-bound concentrations leads to an overestimate of intake and application of lower-bound concentrations to an underestimate of intake. Therefore, the Committee recommended that laboratories report their results as lower-bound, upper-bound, and half-detection limits, in addition to values for individual congeners. In that way, all the necessary information is available for interpreting the results for specific requirements. At a minimum, it should be clear which concept was used. Experts who are summarizing results based on TEQs should consider the way in which the TEQs were calculated and indicate this in their reports.

For reliable analysis of food samples with normal background contamination, gas chromatography/high-resolution mass spectrometry (GC/HRMS) has been validated in collaborative studies and has been shown to provide the required sensitivity and specificity. Bioanalytical assays have been developed for rapid screening in sediments, soil, fly ash, and various foods, but only the chemical-activated luciferase gene expression (CALUX) assay has been used for food, and first steps of validation have been undertaken. While GC/MS is the most powerful method for identification and quantification of congeners and recognition of congener-specific patterns, it does not provide in a matrix a direct measure of the total toxicity of all congeners that act through the Ah-receptor pathway. The CALUX assay provides an indication of the TEQs present in a certain matrix, including interactive (synergistic or antagonistic) effects; however, it cannot provide information on the congener pattern.

The Committee recognized that the available analytical data for PCDDs, PCDFs, and coplanar PCBs are hampered by the lack of generally accepted criteria for intra-laboratory validation and validation procedures that would permit comparison of results from different laboratories. A mutual acceptance of analytical methods would be facilitated by collaborative studies and proficiency testing programs on an international level. For reliable analysis in the range of normal background contamination, laboratories must use sufficiently sensitive methods for control. General statistical parameters that have been established in other fields of residue analysis could provide orientation. The requirements for acceptable analytical methods clearly need to be harmonized so that data are comparable and may be used for risk management purposes.

Levels and patterns of contamination of food commodities

Data were submitted by Belgium, Canada, Japan, New Zealand, Poland, and the USA and by the European Commission in a report based on data for Belgium, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Sweden, and the United Kingdom. In all countries in which a substantial number of samples had been analysed, the concentrations of PCDDs, PCDFs, and coplanar PCBs in food decreased until the late 1990s, but this decrease had slowed or was even partly reversed recently in some food categories in several countries owing to contamination of animal feed. In addition, at the end of the 1990s, the measures taken to reduce contamination at source initiated at the beginning of the decade had a weaker effect than they had earlier. For the present assessment of intake at the international level, only data collected after 1995 were considered.

As the Committee did not have access to the original analytical results, the concentrations used in the assessment were expressed as the sum of congeners. Consequently it was not possible to identify whether the results were obtained by the lower- or upper-bound approach (see previous section).

Insufficient individual data were available from most countries for construction of a full distribution curve of concentrations, and most were submitted in an aggregated format. As recommended by a FAO/WHO workshop on assessing exposure to contaminants, aggregated data were weighted as a function of the number of initial samples and then used to obtain a weighted mean concentration of PCDD/PCDFs and PCBs in 6 major food groups – meat and meat products, eggs, fish and fish products, milk and milk products, vegetables and vegetable products, and fats and oils. National data were therefore aggregated by region or country (Western Europe, North America, New Zealand, Japan), which are summarized in Table 4. Insufficient data were available for the rest of the world to permit a realistic estimate of distribution of contaminants. The Committee recognized that significant differences occur within the food categories in Table 4, and that the data used in this analysis may not reflect the true mean for a food category. For example, mean PCDD, PCDF, and coplanar PCB levels as well as consumption rates vary considerably across fish species, and it was not possible to determine if the mean represents the fish species most commonly consumed. However the data received were not sufficient to allow a more detailed analysis to adequately account for this variation.

In a second step, a log-normal distribution of contaminants in foods was assumed, and a model of distribution was constructed from the weighted mean and a geometric standard deviation of 3 derived from concentrations in six broad food groups. Based on these derived distributions, the percentiles were determined and the derived median values (50^{th} percentile) are presented in Table 4.

Food consumption and dietary intake assessment

Because of the long half-lives of PCDDs, PCDFs, and coplanar PCBs, their health hazard can be estimated only after consideration of intake over a period of months. Short-term variations in PCDD, PCDF, and coplanar PCB concentrations in foods have much less effect on overall intake than might be the case for other food contaminants.

The distribution of long-term mean intake in various populations was calculated using the following procedure:

(1) The distributions of concentrations were constructed for various regions and food groups from the available data. The distributions were assumed to be log-normal.

(2) Data on food consumption from the GEMS/Foods regional diets and national surveys were used to estimate mean consumption for six major food groups for each different diet. A log normal distribution was constructed from these data with a geometric standard deviation of 1.3 extrapolated from the Dutch food consumption survey to account for inter-individual variation in consumption. The average contribution of the six basic food groups to the total food consumption were also derived for each diet.

(3) The dietary intake of a particular population was assessed by combining the concentration and food consumption distributions for that population in a Monte Carlo approach. In each Monte Carlo trial, dietary intake was estimated by multiplying random values for food consumption and concentrations in various food groups. The concentrations were weighted according to the fraction that the food group contributed to total food consumption. The collected intake estimates thus formed a distribution of long-term mean dietary intake for each population studied. The distributions are characterized by the median and the 90th percentile intake. The calculations were performed for the sums of the TEQs of PCDDs/PCDFs and of coplanar PCBs separately, because the data on occurrence were obtained independently.

Table 4. Weighted mean and derived median of concentrations of PCDDs, PCDFs, and coplanar PCBs in six food groups expressed as TEQs (pg/g whole food)

Region or country	Food category	PCDD/PCDFs		coplanar PCBs	
		Weighted mean	Derived median	Weighted mean	Derived median
Western Europe	Dairy	0.07	0.04	0.08	0.07
	Eggs	0.16	0.15	0.07	0.06
	Fish	0.47	0.31	2.55	0.90
	Meat	0.08	0.06	0.41	0.08
	Vegetable products	0.04	0.03	0.04	0.00
Japan	Dairy	0.06	0.04	0.04	0.02
	Eggs	0.07	0.03	0.06	0.04
	Fish	0.37	0.11	0.69	0.19
	Meat	0.09	0.01	0.04	0.009
	Vegetable products	0.003	0.002	0.02	0.003
North America	Dairy	0.10	0.07	0.02[a]	0.01[a]
	Eggs	0.17	0.14	0.04[a]	0.02[a]
	Fish	0.56	0.28	0.13[a]	0.08[a]
	Meat	0.13	0.10	0.14[a]	0.05[a]
New Zealand	Dairy	0.02	0.02	0.01	0.008
	Fish	0.06	0.05	0.09	0.07
	Meat	0.01	0.01	0.02	0.01
	Vegetable products	0.008	0.008	-	-
All	Fats and oils	0.21	0.10	0.07[a]	0.02[a]

[a] PCB data frequently did not include mono-ortho PCBs

The simulated intakes of PCDD/PCDFs and coplanar PCBs based on the GEMS/Food diets are presented in Table 5. However, in general the estimated intakes in Table 5 overestimate the real intake levels, because the concentration data partly consist of surveillance data (surveillance data are not randomly sampled), and GEMS/Food diets are based on food supply (apparent consumption) data which are known to overestimate food consumption by at least 15%.

More reliable estimates of intake (Table 6) were obtained by using national food consumption data rather than food supply (apparent consumption) data from the GEMS/Foods regional diets. The simulated intakes presented in Table 6 are not strictly national estimates and are somewhat higher than the national estimates submitted by European Union Member States.

The calculated contributions of various food categories to the intake of PCDDs, PCDFs, and coplanar PCBs showed that the largest fraction (> 70%) is from food of animal origin in both the GEMS/Foods regional and national diets.

Table 5 Median and 90th percentile of estimated long term intakes of TEQs (pg/kg bw per month, assuming 60 kg bw) based on the GEMS/Foods regional diets

Source of concentration data[a]	Source of food consumption data	PCDD/PCDFs		Coplanar PCBs	
		Median	90th percentile	Median	90th percentile
Western Europe	European	54	130	57	150
North America	European	68	160	14	35
New Zealand	European	18	36	10	22
Japan	Far Eastern	7	15	7	19

[a]for North America the concentration data of vegetables from western Europe were used; for New Zealand the concentration data of eggs from Japan were used.

Table 6. Median and 90th percentile of estimated long term intakes of TEQs (pg/kg bw per month, assuming 60 kg bw) based on national food consumption data

Source of concentration data[a]	Source of food consumption data	PCDD/PCDFs		coplanar PCBs	
		Median	90th percentile	Median	90th percentile
North America	USA	42	100	9	25
Western Europe	Netherlands	33	81	30	82
Western Europe	France	40	94	47	130
Western Europe	United Kingdom	39	91	41	110

[a]for North America the concentration data of vegetables from western Europe were used.

Information was lacking on both the quality and geographic representativeness for some regions. More data are required on the occurrence of coplanar compounds in food products, particularly from geographic regions other than Europe for more representative intake estimates for all regions.

Breast-fed infants have higher intakes of these compounds on a body-weight basis, although for a small portion of their life-spans. Breast milk has beneficial effects, despite the contaminants present. WHO has therefore repeatedly evaluated the health significance of contamination of breast milk with coplanar compounds. WHO recommends and supports breast feeding but has concluded that continued and enhanced efforts should be directed towards identifying and controlling environmental sources of these substances.

Evaluation

In view of the long half-times of PCDDs, PCDFs, and coplanar PCBs, the Committee concluded that it would not be appropriate to establish an acute reference dose for these compounds.

The Committee concluded that a tolerable intake could be established for 2,3,7,8-TCDD on the basis of the assumption that there is a threshold for all effects, including cancer. Carcinogenicity due to 2,3,7,8-TCDD was not linked to mutagenicity or DNA binding, and it occurred at higher body burdens in animals than other toxic effects. The Committee concluded that the establishment of a tolerable intake based on non-cancer effects would also address any carcinogenic risk.

The studies listed in Table 3 were those considered by the Committee in choosing the lowest LOELs and NOELs for assessment of tolerable intake. The lowest LOEL was provided by the study of Faqi et al. (1998) and a NOEL was provided by the study of Ohsako et al. (2001). With the toxicokinetic conversions described in Table 7, these two studies indicate maternal body-burden LOELs and NOELs for effects on male rat offspring of 25 ng/kg bw and 13 ng/kg bw, respectively. The conversion is shown in full in Table 7.

Background body burdens in laboratory animals

In the studies used to estimate body burden on the basis of the distribution of TCDD after multiple dosing, radiolabelled material was used. Therefore, the known background concentrations of TCDD and other PCDDs and PCDFs in the tissues of laboratory rodents resulting from traces of these compounds in rat feed were ignored. The Committee identified two studies that could be used to predict body burdens of rats resulting from the presence of coplanar compounds in laboratory feed. These studies were mutually consistent and predicted that 'unexposed' laboratory rats had TEQ body burdens of 3-12 ng/kg bw, depending on age. Thus, the maternal body burdens of TCDD based on studies with radiolabelled material should be adjusted upward by a minimum of 3 ng/kg bw to account for the background of unlabelled PCDDs and PCDFs. This may still tend to underestimate the maternal TEQ body burden, since 3 ng/kg bw was the minimum in the two studies, and in one of the studies coplanar PCB compounds were not included.

Addition of 3 ng/kg bw to the body burdens calculated using the linear model for the data in Table 2 results in estimated total TEQ body burdens of 16 ng/kg bw for the NOEL of Ohsako et al. (2001) and 28 ng/kg bw for the LOEL identified by Faqi et al. (1998). These body burdens correspond to equivalent human monthly intakes (EHMI) of 240 and 420 pg/kg bw, respectively. Using the power model for the data in Table 2 the EHMIs were 330 pg/kg and 630 pg/kg, respectively.

Identification of safety factors

Safety factors typically considered in establishing acceptable levels of intake on the basis of results of animal studies usually include 1) a factor to convert a LOEL to a NOEL (if needed), 2) a factor to extrapolate from animals to humans, 3) and factors to account for inter-individual variations in susceptibility. Factors of 10 have been used traditionally for interspecies extrapolation and human variability and a factor of 3 to 10 for extrapolating from a LOEL to a NOEL.

A NOEL was identified for effects in the offspring of male rats; thus, no factor for conversion from NOEL to LOEL was needed for the EHMI derived from the Ohsako et al. 2001 study.

As concluded by the 1998 WHO consultation, use of body burdens to scale doses from animal studies to equivalent human levels removes the need for safety factors for toxicokinetic differences between animals and humans.

To account for inter-individual differences in toxicokinetics among humans, a safety factor should be applied. The Committee noted that limited data were available on the toxicokinetics of 2,3,7,8-TCDD in humans, and considered that the default factor of 3.2 was appropriate.

The Committee observed that humans may be less sensitive than rats to some effects, but the conclusion is less certain for others, and it cannot be excluded that the most sensitive humans might be as sensitive to the adverse effects of 2,3,7,8-TCDD as rats were in the pivotal studies. Therefore, the Committee concluded that no safety factor in either direction needs to be applied for differences in toxicodynamics among humans.

Use of a LOEL instead of a NOEL indicates the need for an additional safety factor. As the LOEL reported by Faqi et al. (1998) for the sensitive end-point was considered to be close to a NOEL and represented marginal effects, the Committee applied a factor of 3 to account for use of a LOEL instead of a NOEL. This leads to an overall safety factor of 9.6 (3 x 3.2).

The Committee concluded that a total safety factor of 3.2 should be applied to the EHMI associated with the NOEL identified by Ohsako et al. (2001) and a total safety factor of 9.6 should be applied to the EHMI associated with the LOEL identified by Faqi et al. (1998).

Tolerable intake

As stated previously in the discussion of toxicokinetics, the long half-times of PCDDs, PCDFs, and coplanar PCBs result in each daily ingestion having a small or even negligible effect on overall intake. Only after consideration of the total or average intake of PCDDs, PCDFs, and coplanar PCBs over months can their long- or short-term risk to health be assessed. The tolerable intake should therefore be assessed over 1 month or longer. To encourage this view, the Committee decided to express the tolerable intake as a monthly value in the form of a *provisional tolerable monthly intake*[2] (PTMI).

As shown in Table 7, use of the linear model to extrapolate the maternal body burden at the NOEL in the study of Ohsako et al. (2001) with a single dose to that expected at multiple doses shows that the EHMI expected to produce a body burden that is below that which had effects in animals is 237 pg/kg bw. The PTMI derived by application of the safety factor of 3.2 to this EHMI is 74 pg/kg bw.

Similarly, as presented in Table 7, the PTMI derived by application of the safety factor of 9.6 to the EHMI derived from the study by Faqi et al. (1998) is 44 pg/kg bw.

As also shown in Table 7, use of the power model to extrapolate the maternal body burden with single doses to multiple doses would result in PTMIs of 103 pg/kg bw for the NOEL of Ohsako et al. (2001) and 66 pg/kg bw for the LOEL of Faqi et al. (1998).

The range of PTMIs derived from the two studies, with either the linear or the power model to extrapolate the maternal body burden with single to multiple doses, is 40 to 100 pg/kg bw per month. The Committee chose the midpoint of this range, 70 pg/kg bw per month, for the PTMI. Furthermore, on the basis of the 1998 WHO consultation the Committee concluded that this tolerable intake should be applied to intake of PCDDs, PCDFs, and coplanar compounds expressed as TEFs.

Table 7. Summary of four calculations of PTMI

	Linear model		Power model	
	Ohsako	Faqi	Ohsako	Faqi
Administered dose (ng/kg bw)	12.5[a]		12.5[a]	
Maternal body burden (ng/kg bw)	7.6	25	7.6	25
Equivalent Maternal BB with long-term dosing (ng/kg bw)	13[c]	25[c]	19[d]	39[d]
Body burden from feed (ng/kg bw)	3	3	3	3
Total body burden (ng/kg bw)	16	28	22	42
EHMI (pg/kg bw/month)	237	423	330	630
Safety factor	3.2	9.6	3.2	9.6
PTMI (pg/kg bw/month)	74	44	103	66

[a]Bolus dose (NOEL).
[b]Target maternal body burden from repeated dosing (LOEL).
[c]Assumes a linear relationship between fetal and maternal body burden (based on data in Table 2).
[d]Assumes a non-linear relationship between fetal and maternal body burden (based on data in Table 2).
[e] Assumes, for humans, 7.6 year half-time and 50% uptake from food (Equation 1).

Comparison of PTMI with estimated intake from food

In the GEMS/Food regional diets, the range of estimated intake of TEQs for PCDDs and PCDFs is 7-68 pg/kg bw per month at the median and 15-160 pg/kg bw per month at the 90th percentile of mean lifetime exposure, and those for coplanar PCBs were 7-57 pg/kg bw per month at the median and 19-150 pg/kg bw per month at the 90th percentile of consumption. The intakes estimated from national food consumption data were lower: 33-42 pg/kg bw per month at the median and 81-100 pg/kg bw per month at the 90th percentile for PCDDs and PCDFs, and 9-47 pg/kg bw per month at the median and 25-130 pg/kg bw per

[2] By analogy with the PTWI, the end-point used for safety evaluations by JECFA for food contaminants with cumulative properties. Its value represents permissible human monthly exposure to those contaminants unavoidably associated with otherwise wholesome and nutritious foods.

month at the 90th percentile for coplanar PCBs. Estimates could not be made for the sum of PCDDs, PCDFs, and PCBs, because data on concentrations were submitted separately by countries.

The median and 90th percentile of the derived distribution of intakes were considered to describe long-term intake. A Monte Carlo calculation was used to predict these intakes for coplanar compounds on the basis of two sets of distribution curves generated from information on mean concentrations in six major food groups and corresponding data on mean food consumption from several sources, by applying geometric standard deviations of 3 and 1.3 to the respective means. The geometric standard deviation for the food consumption curves accounted for long-term consumption patterns. As the mean intakes of the whole population tend not to change with the duration of a survey, use of mean consumer intakes to generate the curves for major food groups, rather than individual commodities, approximates the mean intakes of the whole population, as nearly all respondents were consumers.

Uncertainties

Several sources of uncertainty were identified in the data used to assess intake, which suggest that they are likely to be overestimates at both the median and the 90th percentile level of consumption. Despite the uncertainties, the results suggest that a considerable fraction of the population will have long-term mean intake above the PTMI.

Furthermore, despite the large amount of information on toxicity, substantial uncertainties remain which should be considered in applying the risk assessment and interpreting the estimates of intake of PCDDs, PCDFs, and coplanar PCBs. The Committee used the overall data to identify a level of intake of coplanar compounds in food that represents no appreciable risk to humans. The safety assessment includes adjustment for a number of uncertainties, including estimates of TEF values within orders of magnitude to relate the potency of 28 relatively poorly studied compounds to that of one well-studied compound, 2,3,7,8-TCDD. Moreover, the proportion of 2,3,7,8-TCDD in relation to the other 28 compounds varies, typically constituting a small percentage of the total TEQ exposure in foods.

The PTMI is not a limit of toxicity and does not represent a boundary between safe intake and intake associated with a significant increase in body burden or risk. Long-term intakes slightly above the PTMI would not necessarily result in adverse health effects but would erode the safety factor built into the calculations of the PTMI. It is not possible given our current knowledge to define the magnitude and duration of excess intake that would be associated with adverse health effects.

Effect of maximum limits on intake, risk, and food availability

The concentrations of PCDDs, PCDFs, and coplanar PCBs vary within foods. In establishing regulatory limits for them, the possible undesired consequences of their enforcement should be taken into account, for example reductions in the food supply. The Committee explored the theoretical effect of various maximum regulatory limits on compliance and on long-term average reduction of intake require. On the basis of this analysis the Committee concluded that to achieve, for example, a 20% reduction in food-based intake of coplanar compounds one would need to decrease intake of a wide range of foods by a similar percentage. This relationship exists because these contaminants are present at relatively high levels across major food types. Furthermore, in view of the half-times of these compounds in humans, setting regulatory limits on the basis of the PTMI would have no discernible effect on body burdens for several years.

In contrast, long-term reductions could be gained by identifying and eliminating pathways from the environment to food supplies. The Committee was informed that in several countries studies of environmental levels over time suggest that measures taken to control emissions to the environment generally have had a substantial impact on both the amounts of PCDDs and PCDFs present in the environment and the body burdens of the general public.

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Research Article

Concentration-dependent TCDD elimination kinetics in humans: toxicokinetic modeling for moderately to highly exposed adults from Seveso, Italy, and Vienna, Austria, and impact on dose estimates for the NIOSH cohort

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Abstract

Serial measurements of serum lipid 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) concentrations in 36 adults from Seveso, Italy, and three patients from Vienna, Austria, with initial serum lipid TCDD concentrations ranging from 130 to 144,000 ppt, were modeled using a modified version of a previously published toxicokinetic model for the distribution and elimination of dioxins. The original model structure accounted for a concentration-dependent increase in overall elimination rate for TCDD due to nonlinear distribution of TCDD to the liver (secondary to induction of the binding protein CYP1A2), from which elimination takes place via a first-order process. The original model structure was modified to include elimination due to lipid partitioning of TCDD from circulation into the large intestine, based on published human data. We optimized the fit of the modified model to the data by varying the hepatic elimination rate parameter for each of the 39 people. The model fits indicate that there is significant interindividual variability of TCDD elimination efficiency in humans and also demonstrate faster elimination in men compared to women, and in younger vs. older persons. The data and model results indicate that, for males, the mean apparent half-life for TCDD (as reflected in changes in predicted serum lipid TCDD level) ranges from less than 3 years at serum lipid levels above 10,000 ppt to over 10 years at serum lipid levels below 50 ppt. Application of the model to serum sampling data from the cohort of US herbicide-manufacturing workers assembled by the National Institute of Occupational Safety and Health (NIOSH) indicates that previous estimates of peak serum lipid TCDD concentrations in dioxin-exposed manufacturing workers, based on first-order back-extrapolations with half-lives of 7–9 years, may have underestimated the maximum concentrations in these workers and other occupational cohorts by several-fold to an order of magnitude or more. Such dose estimates, based on a single sampling point decades after last exposure, are highly variable and dependent on a variety of assumptions and factors that cannot be fully determined, including interindividual variations in elimination efficiency. Dose estimates for these cohorts should be re-evaluated in light of the demonstration of concentration-dependent elimination kinetics for TCDD, and the large degree of uncertainty in back-calculated dose estimates should be explicitly incorporated in quantitative estimates of TCDD's carcinogenic potency based on such data.

Keywords

TCDD; elimination kinetics; human; toxicokinetic modeling

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